Summer 7-31-2019

Phosphonate-Directed Catalytic Asymmetric Hydroboration: Synthesis of Functionalized Chiral Secondary and Tertiary Boronic Esters and Mechanistic Insights

Suman Chakrabarty
University of Nebraska - Lincoln, suman.chakrabarty@huskers.unl.edu

PHOSPHONATE-DIRECTED CATALYTIC ASYMMETRIC HYDROBORATION: SYNTHESIS OF FUNCTIONALIZED CHIRAL SECONDARY AND TERTIARY BORONIC ESTERS AND MECHANISTIC INSIGHTS

by

Suman Chakrabarty

A DISSERTATION

Presented to the Faculty of

The Graduate College at the University of Nebraska

In Partial Fulfillment of Requirements

For the Degree of Doctor of Philosophy

Major: Chemistry

Under the Supervision of Professor James M. Takacs

Lincoln, Nebraska

United States

July 2019

PHOSPHONATE-DIRECTED CATALYTIC ASYMMETRIC HYDROBORATION: SYNTHESIS OF FUNCTIONALIZED CHIRAL SECONDARY AND TERTIARY BORONIC ESTERS AND MECHANISTIC INSIGHTS

Suman Chakrabarty, Ph.D.

University of Nebraska, 2019

Advisor: James M. Takacs

Over the past 30 years, catalytic asymmetric hydroboration (CAHB) of alkenes has emerged as a leading methodology to access chiral primary and secondary boronic esters. However, it wasn't until 2015 that directed-CAHB was for the first time shown to efficiently access chiral tertiary boronic esters. The latter are excellent precursors to synthetically challenging structural motifs such as chiral tertiary alcohols, carbinamines and all-carbon quaternary stereocenters via stereospecific C-B bond substitutions. This dissertation focuses on phosphonate-directed CAHB of diverse alkene substrates, including challenging stereodefined trisubstituted alkenes, to efficiently access multifunctional chiral secondary and tertiary boronic esters. Mechanistic insights obtained via deuterium labelling experiments indicate that CAHB reactions proceed via tertiary-alkyl rhodium intermediates for substrates that lead to chiral tertiary boronic esters. The applications of phosphonate-functionalized chiral secondary and tertiary boronic ester products are discussed in the context of stereospecific C-B bond transformations, through phosphonate unmasking methodologies via thiophosphonate and oxophosphonate intermediates, and through synthesis of the cytotoxic natural product bakuchiol.

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my Ph.D. advisor, Prof. James Takacs for providing me with the opportunity to work in his research group and enabling me with all the necessary resources to complete my research projects. He provided enormous freedom in terms of planning and designing research projects and was always willing to talk and provide suggestions for successful execution of experiments. He would constantly encourage us to attend several national and international conferences/meetings to present our research. I had a lot of fun learning new science and making friends and collaborations in several of these conferences. I am also thankful to Dr. Takacs for nominating me for the Cliff S. Hamilton and Norman H. Cromwell graduate student awards, and also for nominating me for the position of an organic chemistry instructor that was open in the department of chemistry at UNL in fall 2018. I eventually got the position and being an instructor-of-record for a second semester organic chemistry course for a group of 115 students majoring in biochemistry and other related majors was an outstanding experience. In addition to chemistry, I learned a lot of practical and life lessons from Prof. Takacs, several of which I will carry with myself for life.

I thank my supervisory committee members Dr. Patrick Dussault, Dr. Liangcheng Du, Dr. Alexander Sinitskii and Dr. Stephen Ducharme for their involvement in my Ph.D. career. I am grateful to Dr. Dussault for writing recommendation letters on my behalf for postdoctoral positions and for the graduate courses on *Organic and Bioconjugate Reactions* and *Advanced Synthetic Strategies*. Dr. Du was my immediate boss when I was teaching CHEM 252 in Fall 2018 and I am thankful to him for his guidance and help even on the toughest of days. I am also grateful to Dr. Du for writing recommendation letters on my

behalf for postdoctoral positions and for the graduate course on *Biosynthesis of Natural Products*. Other professors and staff members in the chemistry department have been extremely supportive and helpful through my time at UNL: Dr. Richard Hartung, Dr. Chris McCune, Dr. Martha Morton, Deanna Larson, DeNeice Steinmeyer, Leanna Klempa, Dodie Eveleth, Kate Shaner, Rene Barfoot, Robert Wilson, Kurt Wulser, Peg Bergmeyer and several others-it was a pleasure knowing you all and to work with all of you. I am thankful to Dr. Dussault and his group members Alissa Horn and Moriah Locklear for help with ozonolysis experiments and Dr. Ronald Cerny and Kurt Wulser for assistance with high resolution mass spectral analysis. I am thankful to the Chemistry department for the travel fellowship to attend the 249th ACS National Meeting in Denver CO, and to the Hamilton family and Cromwell foundation for the fellowships I received due to their generous donations.

During my time in the Takacs group, I had the opportunity to work with terrific individuals who were fiercely driven and passionate about doing chemistry! I am thankful to Dr. Nathan C. Thacker, Dr. Gia L. Hoang and most importantly to Dr. Kostiantyn O. Marichev for training and mentoring me during my first year in the graduate program. Dr. Veronika M. Shoba and I had the maximum overlap during my time in graduate school and we developed close friendship during this time. I am thankful to several people from the Takacs group that I had the opportunity to work with over the years: Dr. Hector Palencia, Dr. Libby Pelter, Dr. Kazuya Toyama, Dr. Tanner Metz, Andy Geis, Shuyang Zhang, Peter Reitgraf, Ryan Carr, Andrew Bochat and Rukshani Wickrama-Arachi. I wish you all good luck with your current and future endeavors.

I was lucky to make several friends in Lincoln that were present for me through good and bad times over the years. I am thankful to Alexander Pages, Shelley Freeman, Paul Freeman, Kimberly Pella and Melissa Pella. I am particularly grateful to Alex, Shelley and Paul for taking care of me when I was admitted to Bryan Health for the emergency appendectomy. I will miss the time spent with the Pellas on Sunday evenings watching Game of Thrones together.

I would like to have a special mention of my school teachers and college professors that have inspired me through the years. I am thankful to Ms. L. M. Chacko and Ms. K Mazumder in SEREMS (Chakradharpur), Fr. Ajit Kr. Xess, Ms. Indira Bhattacharya, Ms. Indrani Chatterjee, Ms. Mani Sinha and several others in St. Xavier's School (Ranchi), Dr. Melwin Colaco, Dr. Ronald Mascarenhas, Dr. Mohan Das, Dr. Sandra Misquith, Dr. Mithra Madappa, Dr. Grace Prabhakar, Dr. Betty Daniel and several others in St. Joseph's College (Bangalore), Dr. Riya Datta, Dr. Susan Abraham, Dr. Aatika Nizam, Dr. N M. Nanje Gowda and several others at Christ University (Bangalore) for mentoring me through the years!

Finally, I would like to thank my parents Shila Chatterjee and Swapan K. Chakrabarty and my brother Saurabh Chakrabarty for having my back and for supporting me in every step of my career.

COPYRIGHT DISCLAIMER

Parts of the research work compiled in this dissertation are published separately in three different academic research journals which are listed below:

(1). Chakrabarty, S.; Palencia, H.; Morton, M. D.; Carr, R. O.; Takacs, J. M. *"Facile access to functionalized chiral secondary benzylic boronic esters via catalytic asymmetric hydroboration"*, *Chem. Sci.,* **2019**, *10*, 4854-4861. DOI: 10.1039/C8SC05613G. Copyright © The Royal Society of Chemistry 2019

(2). Chakrabarty, S.; Takacs, J. M. *"Phosphonate-Directed Catalytic Asymmetric Hydroboration: Delivery of Boron to the More Substituted Carbon, Leading to Chiral Tertiary Benzylic Boronic Esters"*, *ACS Catal.*, **2018**, *8*, 10530-10536. DOI: 10.1021/acscatal.8b03591. Copyright © 2018 American Chemical Society

(3). Chakrabarty, S.; Takacs, J. M. *"Synthesis of Chiral Tertiary Boronic Esters: Phosphonate-Directed Catalytic Asymmetric Hydroboration of Trisubstituted Alkenes"*, *J. Am. Chem. Soc.,* **2017**, *139*, 6066-6039. DOI: 10.1021/jacs.7b02324. Copyright © 2017 American Chemical Society

NOTICE TO THE READER: Copyright permission was obtained from each of the three journals cited above for reproduction of the entire content of each manuscript in this dissertation. The publication sources are cited for each reproduction of the original content (text/figures) made in this dissertation. For further permissions related to the material(s) excerpted, the reader should direct further permissions to the respective journal in which the work is published. Copyright for unpublished work is reserved by the author.

PREFACE

This dissertation comprises of five chapters: (1) Introduction; (2) Phosphonate-Directed Catalytic Asymmetric Hydroboration of Disubstituted Vinyl Arenes; (3) Phosphonate-Directed Catalytic Asymmetric Hydroboration of Trisubstituted Alkenes; (4) Stereospecific Transformations of Phosphonate-Functionalized Chiral Secondary and Tertiary Boronic Esters; (5) Experimental Procedures and Characterization Data.

The first chapter is an introduction to chiral boronic esters-their synthetic, biological and medicinal relevance. In addition, the first chapter entails a comprehensive coverage of the reported methods of enantioselective synthesis of chiral tertiary boronic esters and their stereospecific transformations. The first chapter ends with a section on the introduction to the phosphonate-functionality-their biological relevance and directing properties and the initial goals behind the development of phosphonate-directed catalytic asymmetric hydroboration.

The second chapter details the phosphonate-directed catalytic asymmetric hydroboration results with 1,1- and 1,2-disubstituted vinyl arenes and the mechanistic insights obtained in each case. This chapter includes comparisons of directing groups, effect of distance between the directing group and the alkene, effect of alkene geometry and substrate scope for the two substrate types studied. The second chapter also includes mechanistic investigations via deuterium labelling experiments with pinBD. The results presented in Chapter 2, Sections 2.2, 2.3 and 2.5 are published in the journal ACS Catalysis (*ACS Catal.*, **2018**, *8*, 10530) and sections 2.6-2.10 are published in the journal Chemical Science (*Chem. Sci.*, **2019**, *10*, 4854).

The third chapter begins with a review of the reported methods of efficient CAHB of trisubstituted alkenes in the literature. This chapter covers the phosphonate-directed catalytic asymmetric hydroboration results with all-alkyl, aryl-alkyl and bisaryl trisubstituted alkenes to access chiral tertiary boronic esters. Substrate scope and mechanistic insights via deuterium labelling experiments are included. The results presented in Chapter 3, Sections 3.2, parts of 3.3 and 3.4 are published in the Journal of the American Chemical Society (*J. Am. Chem. Soc.*, **2017**, *139*, 6066), sections 3.5 and 3.7 are published in the journal ACS Catalysis (*ACS Catal.*, **2018**, *8*, 10530).

The fourth chapter is dedicated to the stereospecific transformations carried out with the phosphonate-functionalized chiral boronic esters that are generated using the chemistry. This chapter includes stereospecific C-B bond transformations with chiral secondary benzylic boronic esters, chiral tertiary benzylic boronic esters and chiral tertiary all-alkyl boronic esters. This chapter also covers phosphonate-unmasking via oxophosphonate intermediates and total synthesis of the cytotoxic natural product bakuchiol using Corey's thiophosphonate olefination chemistry. The results presented in Chapter 4, sections 4.2 and 4.3 are published in the journal ACS Catalysis (*ACS Catal.*, **2018**, *8*, 10530), section 4.4 is published in Chemical Science (*Chem. Sci.*, **2019**, *10*, 4854) and sections 4.5 and 4.6 are published in Journal of the American Chemical Society (*J. Am. Chem. Soc.*, **2017**, *139*, 6066).

The last chapter provides experimental procedures for substrate synthesis, for catalytic asymmetric hydroboration and transformations of the derived products. Characterization data for new molecules and absolute configuration assignments are included. Most of the data compiled in chapter 5 is published in the supporting information

sections of the following published journal articles: (i) *Chem. Sci.*, **2019**, *10*, 4854; (ii) *ACS Catal.*, **2018**, *8*, 10530; (iii) *J. Am. Chem. Soc.*, **2017**, *139*, 6066.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF ABBREVIATIONS

Ac	Acetate
acac	Acetylacetonate
aq	Aqueous
Ar	Aryl
BE	Boronic ester
BINAP	2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
BINOL	2,2’-Dihydroxy-1,1’-binaphthyl
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
br s	Broad singlet
Bz	Benzoyl
c	Concentration
CAHB	Catalytic asymmetric hydroboration
catBH	Catecholborane
c-Hex or Cy	Cyclohexyl
cod	Cyclooctadiene
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
dd	Doublet of doublets
dr	Diastereomer ratio

DFT	Density functional theory
DG	Directing group
DIBAL-H	Diisobutylaluminum hydride
DMF	N,N-Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
ee	Enantiomer excess
Equiv	Equivalent
er	Enantiomer ratio
h or hr	Hour
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
IR	Infrared
J	Coupling constant
LDA	Lithium diisopropylamide
m	Multiplet
min	Minutes
ml or mL	Milliliter
ND	Not determined
nbd	Norbornadiene
NBS	N-Bromosuccinimide
NLE	Non-linear effect

NMR	Nuclear magnetic resonance
Nu	Nucleophile
pinBH	Pinacolborane
ppm	Parts per million
rac	Racemic
R_f	Retention factor
s	Singlet
sr	% stereoretention
T	Temperature
t	Triplet or time
TADDOL	α,α,α’,α’-Tetraaryl-1,3-dioxolan-4,5-dimethanol
TBAF	Tetra-butyl ammonium fluoride
TCCA	Trichloroisocyanuric acid
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
tmdBH	4,5,6-Trimethyl-1,3,2-dioxaborinane
UV-Vis	Ultraviolet-visible spectroscopy

CHAPTER ONE: INTRODUCTION

1.1. Introduction to Chiral Boronic Esters: Synthetic, Biological and Medicinal Relevance

Chiral boronic esters, in the context of this dissertation, are derivatives of boronic acids where the C-B bond is attached to the stereogenic carbon atom. These are versatile reagents for diversity-oriented synthesis because they possess a unique blend of bench stability and the potential to undergo a myriad of diverse stereospecific transformations.[1] The C-B bond can be stereospecifically transformed to a C-H, C-C, C-O, C-N and C-X (X = halogen) bonds as shown in the transformation wheel in Figure 1.1.[2]

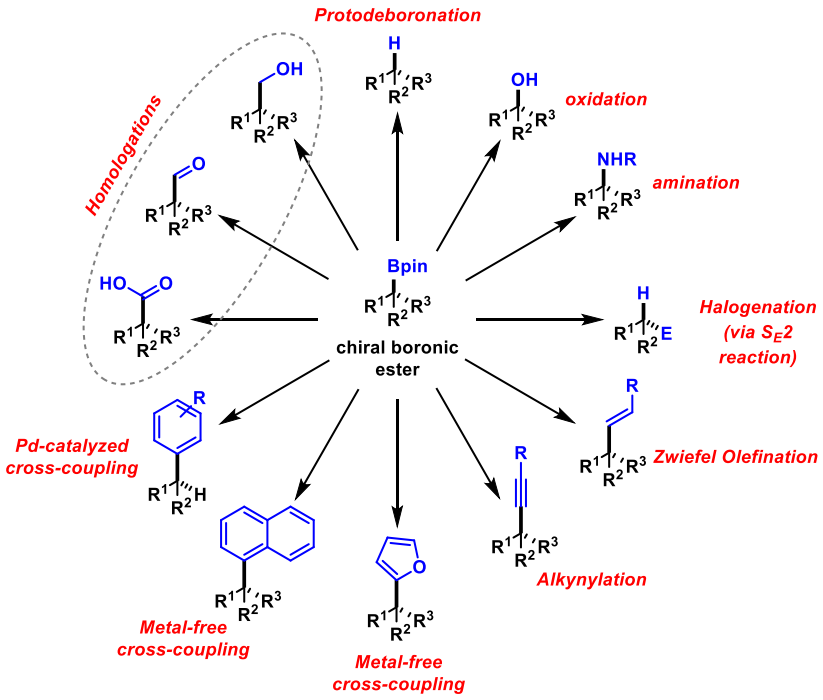


Figure 1.1. Selected Stereospecific transformations of chiral boronic esters.

The unique reactivity of the chiral boronic esters stems from the presence of an empty 2*p*-orbital on boron, rendering it Lewis acidic and therefore susceptible to undergo

addition reactions with nucleophiles which with suitable substituents provides pathways for rearrangement or substitution. For example, oxidation of chiral boronic esters occurs via the initial addition of a peroxide anion into the empty *p*-orbital of boron resulting in a boron *"ate"* complex possessing a weak O-O bond adjacent (Figure 1.2A). The boron-ate complex spontaneously undergoes 1,2-migration with the loss of hydroxide (or more generally a leaving group attached to the initial nucleophilic atom). The final hydrolysis of the O-B bond results in the formation of the alcohol product.

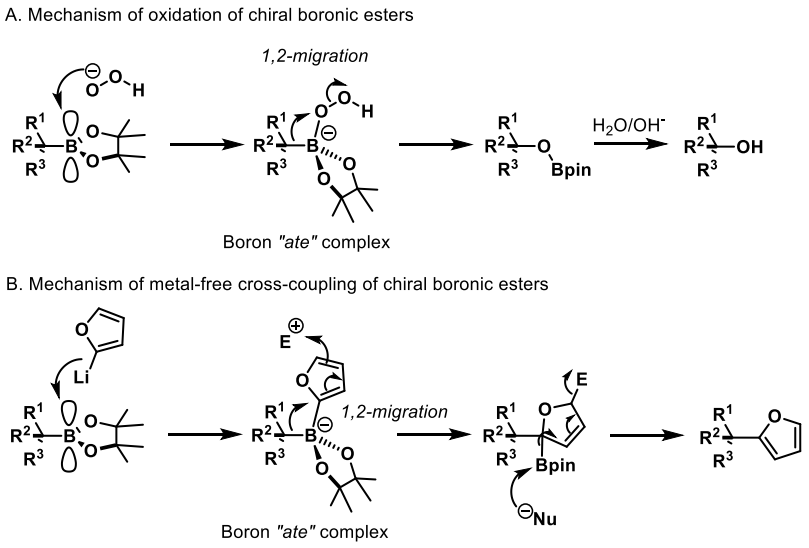


Figure 1.2. Mechanisms of oxidation and metal-free cross-couplings of chiral boronic esters.

A transition metal-free cross-coupling of chiral boronic esters with electron rich aromatics also features a very similar mechanistic pathway (Figure 1.2B).[3] The initial addition of a lithiated aromatic ring to the chiral boronic ester generates an *"ate"* complex, which undergoes the desired 1,2-migration/rearrangement when activated by an electrophile. The intermediate rearomatizes upon subsequent nucleophilic addition to boron with the eventual loss of the electrophile to afford the cross-coupled product. The

1,2-migration (also known as Matteson Rearrangement) from boronate complexes occurs with complete stereospecificity, with the configuration of the carbon atom initially attached to boron retained , a feature common to several boron-based stereospecific transformations.

Chiral boronic esters have been strategically utilized in diversity-oriented synthesis by several groups. Selected examples include the development of an iterative, reagent-controlled homologation of chiral boronic esters in an assembly line-type synthesis to generate complex organic molecules that contain several contiguous methyl bearing stereocenters (Figure 1.3A).[4] This strategy is versatile and has been used to synthesize various diastereomers for molecules bearing multiple chiral centers. This methodology was carried out essentially in a single pot, using continuous homologation processes to synthesize molecules such as (+)-kalkitoxin and (+)-hydroxyphthioceranic acid (Figure 1.3B).[5]

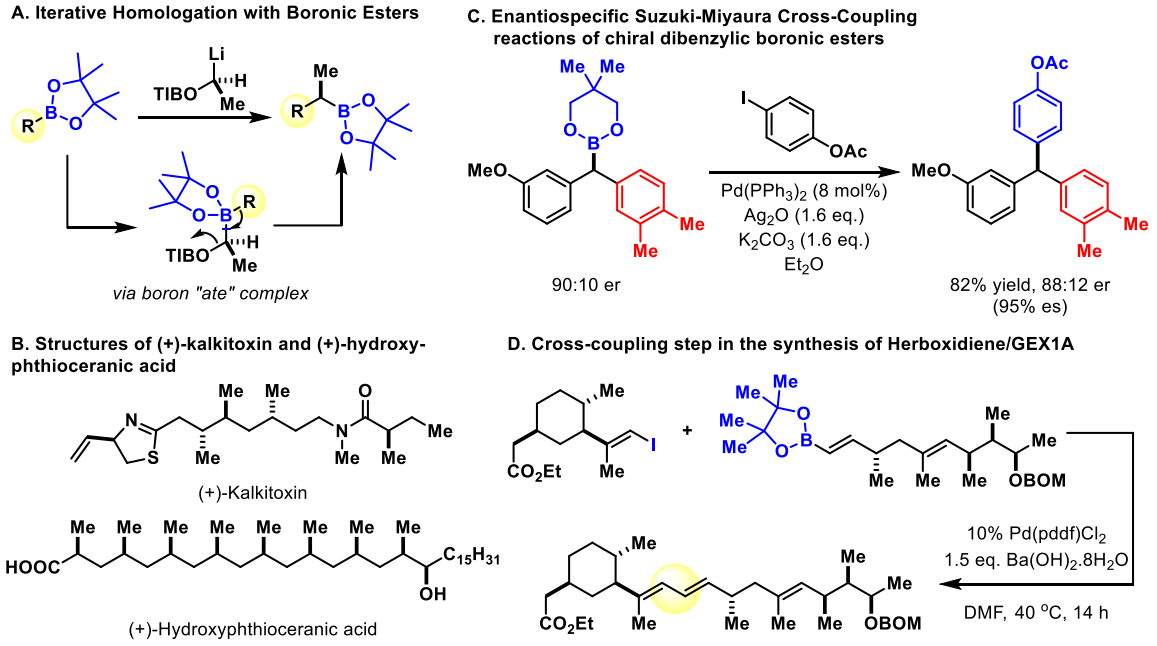


Figure 1.3: Selected examples of utility of chiral boronic esters in asymmetric total synthesis.

Organoboron compounds have found much use in the past few decades such as components in the powerful palladium-catalyzed Suzuki-Miyaura cross-coupling reaction; the latter is one of the widely used reactions in the pharmaceutical industry for constructing C-C bonds.[1,6] The Crudden group developed an efficient method for the enantioselective construction of chiral unsymmetrical triaryl methane derivatives via enantiospecific Suzuki cross-coupling of chiral bisbenzylic boronic esters (Figure 1.3C).[1d] The chiral unsymmetrical triaryl compounds possess potent biological activity and are difficult to prepare via other methods. Yet another example of the utility of chiral boronic esters is in the gram scale synthesis of Herboxidiene/GEX1A developed by the Hoveyda group (Figure 1.4D).[6] A crucial step in the synthesis involves the construction of a C-C bond using palladium-catalyzed cross-coupling between a vinyl boronic ester and a vinyl iodide.

Recent advances in enzyme engineering has expanded nature's catalytic repertoire that are not typically found in biological systems. For example, Frances Arnold's research team has recently disclosed the discovery, evolution and generalization of a fully genetically encoded platform for producing chiral organoboranes in bacteria (Figure 1.5).[7] The team showed that *E. Coli* cells harboring wild-type cytochrome *c* from *Rhodothermus marinus* (*Rma* cyt *c*) could form C-B bonds via carbene insertion into B-H bonds. Directed evolution of *Rma* cyt *c* resulted in the optimization of the reaction for gram-scale biosynthesis of chiral organoboron compounds with a staggeringly high turnover number of 15,300 and a turnover frequency of 6100/h with 100% chemoselectivity and an enantiomer ratio of 99:1 er. The *R*/*S*-enantiopreference of the enzyme could be tuned as well. Arnold's work is the first ever report of catalyzing C-B bond formation using enzymes.

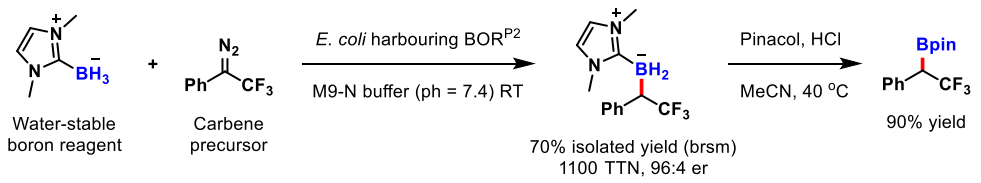


Figure 1.5: Genetically programmed chiral organoborane synthesis: Enzyme-catalyzed construction of C-B bonds.

Boron is less commonly found in nature than carbon, nitrogen, oxygen or even halogens. Although compounds bearing C-B bonds have become extremely useful in synthesis, their presence in nature is unknown. Where present, boron exists in the form of borates (boric acid derivatives) and serves mainly a structural role as a tetrahedral linker between four alkoxide units.[8] Thus, to incorporate boron into biomolecules, microorganisms produce small molecules that spontaneously react with boric acid present in nature. Selected examples of such structures in nature include the boric-acid based macrolide antibiotics boromycin, borophycin, aplasomycins, and tartolons. The antibiotic boromycin was isolated from *Streptomyces antibioticus* in 1967 and it is the first boron-containing natural product that was ever isolated. Boromycin is effective against gram positive bacteria and it does so by negatively affecting the cytosol leading to loss of potassium ions from the cell.[9] Boromycin has also shown anti-HIV activity.[10] Borophycin is a potent cytotoxin isolated from the marine strain of the blue-green algae *Nostoc linckia*.[11] The Tartrolons are boron containing antibiotics from a myxobacterium, *Sorangium cellulosum*.[12] The boron binding region of the Tartrolons are similar to that of boromycin and borophycin. The aplasmomycins were isolated in 1975 from the strain of *Streptomyces griseus* and these showed antibiotic activity against gram positive bacteria

and their structures were related to boromycin. AI-2 is a bacterial signaling molecule containing boron that has been involved in intracellular communication through quorum sensing.[13] The structures of boromycin, borophycin, aplasmomycin A, tartrolon B and are shown in Figure 1.4.

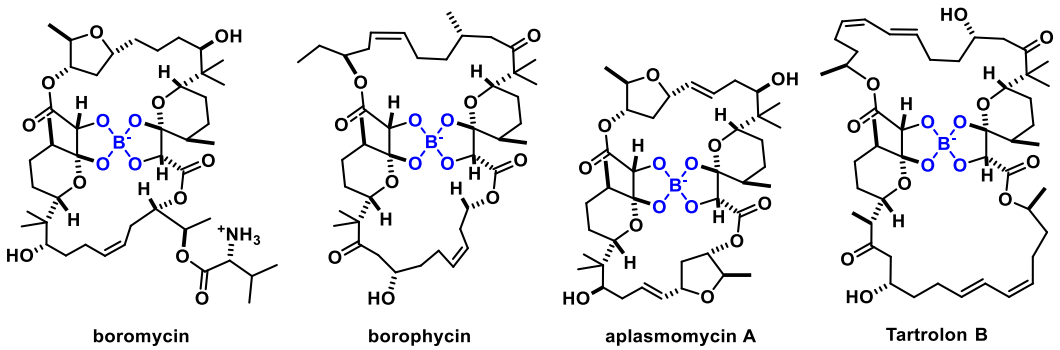


Figure 1.4: Selected examples of boron-containing natural products found in nature.

While considerably less attention was given to boron containing organic compounds for the longest time mainly due to lack of efficient methods to access them, use of boron in the design of pharmaceuticals has a high potential for discovery of new biological activities. Chiral boronic acids and esters are now attracting significant interest as potential therapeutic agents (Figure 1.6).[14] This is mainly due to the specific physical and physiological properties of boron. For instance, the pKa of a boronic acid is about 10 and hence it essentially stays protonated under physiological conditions. Furthermore, the propensity of boronic acids to form hydrogen bonds as well as B-N bonds can enhance protein-ligand interactions. Furthermore, the presence of a vacant *p*-orbital in boron allows for the interconversion between the neutral sp^2 and anionic sp^3 hybridized states, which allows for interconversion between two possible structural states and gives a new platform for drug design. In addition, organoboron compounds are generally air-stable and are of

low toxicity and hence boron has significant potential in the design of therapeutic agents. Selected examples of boron-based pharmaceuticals (as shown in Figure 1.6) are the anticoagulant TRI50c, the anticancer agent Bortezomib[15] used for the treatment of multiple myeloma and non-Hodgkin's lymphoma, the DPP4 inhibitor dutogliptin which has been investigated as an antidiabetic agent, the antiviral drugs based on the template of Bocepvir, the antibacterial agent Benzo[b]thiophene-2-boronic acid was found to have an affinity for *E. coli* and the antifungal cyclic boronic ester AN2690 (tavaborole).[16]

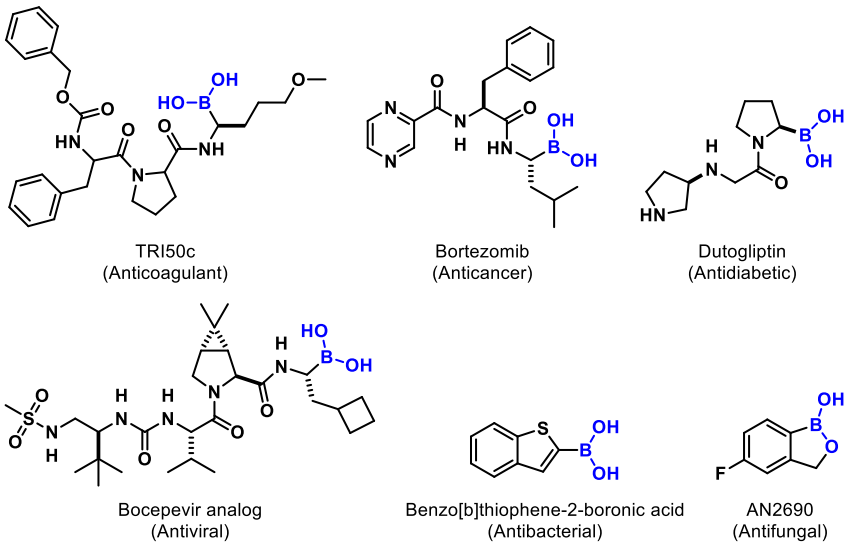


Figure 1.6: Selected examples of boron-based pharmaceuticals.

1.2. Chiral tertiary boronic esters: Introduction and enantioselective synthesis

The discussion above is intended to give a broad, but brief, overview of modern aspects of organoborane research. The dissertation focuses on developing methods to prepare a particular subclass of structures. Chiral structures in which boronic ester functionality is directly attached to a quaternary carbon stereocenter are known as chiral tertiary boronic esters. Nonracemic chiral tertiary boronic esters are excellent precursors to chiral tertiary

alcohols, carbinamines and all-carbon quaternary stereocenters via stereospecific C-B bond substitution.[2] All-carbon quaternary stereocenters are important structural motifs commonly encountered in bioactive natural products and pharmaceutical drugs.[17] The steric encumbrance around a quaternary carbon stereocenter often renders the stereoselective assembly of such molecules a challenging undertaking. Furthermore, the challenge of quaternary carbon stereocenters also results from the lack of hydrogen handles, which limits approaches via reduction or reductive transpositions or via chiral protonation methods. Therefore, development of processes for the enantioselective synthesis of fully substituted carbon stereocenters continues to be one of the major challenges in the field of asymmetric catalysis. Several groups have contributed to the development of methods towards the efficient construction of chiral tertiary boronic esters. These are summarized below.

Matteson reported the first ever synthesis of chiral tertiary boronic esters in 1990.[18] The methodology relied on homologation of a pinanediol-derived chiral boronic ester using (1,1-dichloroethyl)lithium and $ZnCl_2$ to afford the corresponding α-chloro chiral tertiary boronic ester (Figure 1.7).

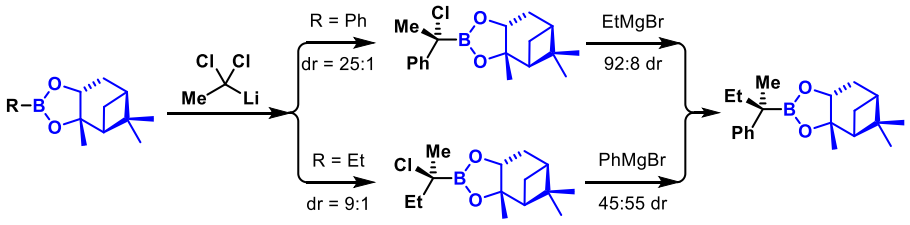


Figure 1.7: Matteson's stereocontrolled synthesis of chiral tertiary boronic esters via stereospecific homologation from pinanediol boronic esters followed by nucleophilic substitution.

Stereospecific substitution from the α-chloro chiral tertiary boronic ester gave the corresponding all-alkyl tertiary boronic ester. The stereochemistry of the formed α-chloro chiral tertiary boronic was found to be dependent on the structure of the starting boronic ester. For example, the phenylboronate leads to the formation of α-(*S*)-α-chloro boronic ester in a diastereomer ratio (dr) of 25:1 upon homologation with lithiodichloromethane. The ethylboronate leads to the formation of α-(*R*)-α-chloro boronic ester in a more modest diastereoselectivity of 9:1 dr. The transformation of α-chloro-phenylboronate to the tertiary all-alkyl boronic ester occurred with only modest loss of diastereopurity, the dr of the final product being 92:8. On the other hand, similar treatment of the α-chloro-ethylboronate with phenylmagnesium bromide occurred with significant loss of enantiopurity.

Several new strategies have been developed for the enantioselective construction of chiral tertiary boronic esters.[19] In contrast to the Matteson approach, most of these involve asymmetric catalysis. In a broad context, there are five unique approaches to access these compounds: (i) lithiation-borylation methodology developed by Aggarwal, [20] (ii) conjugate borylation approaches developed by Shibasaki,[21] Hoveyda,[22] Yun[23,24] and Zhang,[25] (iii) allylic substitution developed by Hoveyda,[26] (iv) conjunctive cross-coupling protocol developed by Morken[27] and (v) asymmetric hydroboration approaches developed by Tang[28] and Takacs.[29,30]

Aggarwal reported the 1,2-metallate rearrangement of boron-ate complexes to assemble chiral tertiary boronic esters in 2008. The 1,2-metallate rearrangement of boron *"ate"* complexes is essentially a 1,2-B-to-C migration (also referred to as the Matteson rearrangement) and this rearrangement forms the basis for several of the stereoretentive transformations of chiral boronic esters.[31] Hoppe's lithiated carbamates derived from chiral

secondary alcohols (carbamate formation followed by treatment with alkyl-lithium bases) were shown to undergo 1,2-B-to-C migration to form chiral tertiary boronic esters in excellent yields and in very high levels of enantioinduction (up to 99:1 er or higher). The Aggarwal group has since reported the synthesis of chiral tertiary all-alkyl,[32] allyl,[33] benzyl,[3] dibenzyl,[34] propargyl[35] and silyl[36] boronic esters via stereospecific 1,2-B-to-C migration protocol (Figure 1.8).

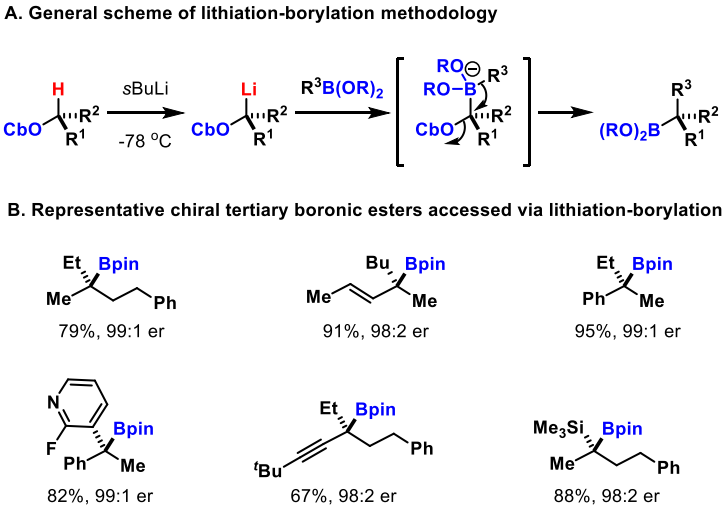


Figure 1.8: Lithiation-borylation strategy to access chiral tertiary boronic esters from carbamates derived from chiral secondary alcohols. A: General scheme of lithiation-borylation methodology. B: Different classes of chiral tertiary boronic esters accessed via lithiation-borylation

---

As noted above, the second approach to prepare chiral tertiary boronic esters, the conjugate borylation of Michael acceptors, has been developed by several researchers. It is perhaps the most common methodology used to access chiral tertiary boronic esters. Conjugate borylation approaches result in a net boron-hydrogen addition across a C–C double bond. These processes are appropriately referred to as protoboration, because the

mechanism involves initial addition of a nucleophilic boryl species (borometallation of the alkene) followed by protonolysis of the formed C-Metal (usually Cu) bond. A ligated boryl-copper intermediate generated via transmetallation of a diboron species (e.g. bispinacolatodiboron $B_2(pin)_2$) with a copper alkoxide acts as the nucleophilic boron species in these reactions (Figure 1.9).[37] Borometallation (often proceeding via a stereospecific and syn addition) adds boron to the more electrophilic β-position of the Michael acceptor substrates leading to the initial formation of a C-Cu bond α-to the electron-withdrawing group, which, depending upon the nature of the substrate undergoing reaction, may further isomerize. Direct protonolysis of the α-C-Cu bond introduces the α-C-H bond, or alternatively the copper enolate (formed in case of enone substrates) can undergo transmetallation with another diboron species to yield the 1,4-diborylated product, which upon aqueous workup hydrolyzes to the observed β-borated product.

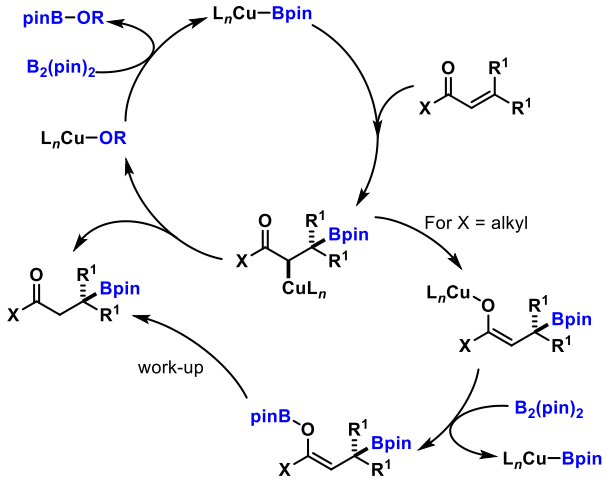


Figure 1.9: Mechanistic rationale for conjugate borylation of Michael acceptors to access chiral tertiary boronic esters.[37]

The net protoboration of Michael acceptors such α,β-unsaturated (i.e., vinyl) ketones, esters, thioesters, nitriles and phosphonates have been carried out using conjugate borylation methodology to allow facile access to the corresponding β-borated chiral tertiary boronic ester products (Figure 1.10).

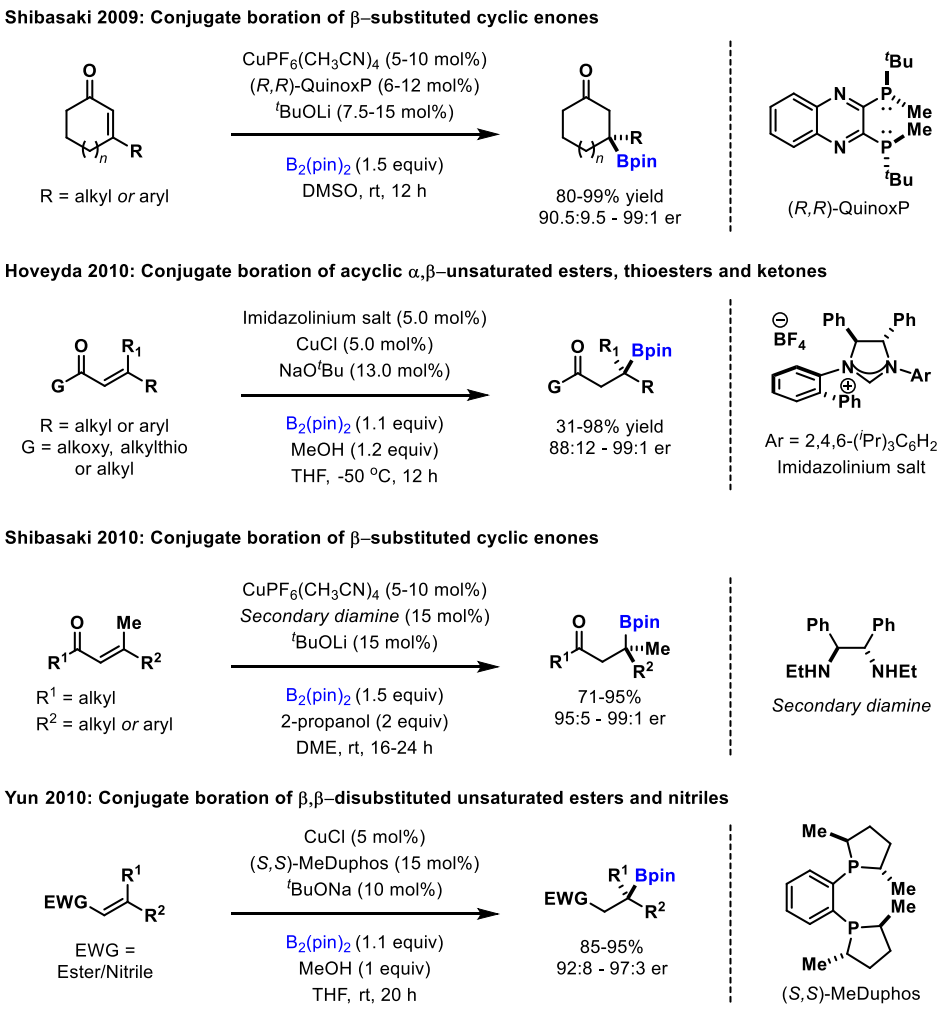


Figure 1.10: Early reports of conjugate boration methodology to access chiral tertiary boronic esters from α,β-unsaturated esters, ketones, thioesters and nitriles.

The groups of Shibasaki,[21] Yun[23] and Hoveyda[22] pioneered the development of copper-catalysts for the conjugate borylation of a variety of substrates

including acyclic/cyclic enones, α,β-unsaturated esters, nitriles and thioesters. The catalyst systems and the reaction conditions for specific substrate types reported by the three groups are significantly different. Chiral bisphosphines, diamines and N-heterocyclic carbenes were used to generate the active catalyst in-situ from appropriate copper precatalysts. Polar aprotic solvents such as DME, DMSO and THF were commonly used along with protic additives in these reactions. It is worth noting, however, that Shibasaki's first report on conjugate borylation does not use any protic additives and adventitious moisture could account for the protonolysis step in the mechanistic cycle.[21]

In 2014, a subsequent report from Hoveyda's group in 2014 disclosed the Lewis-base (N-heterocyclic carbene) catalyzed enantioselective boryl conjugate additions to enones forming chiral tertiary boronic esters.[38] In this protocol, there was no metal catalyst involved and the N-heterocyclic carbene (1-5 mol%) was the only catalyst used. In some cases, this method afforded the desired products with higher selectivity profiles as compared to the corresponding metal-catalyzed variants (Figure 1.11).

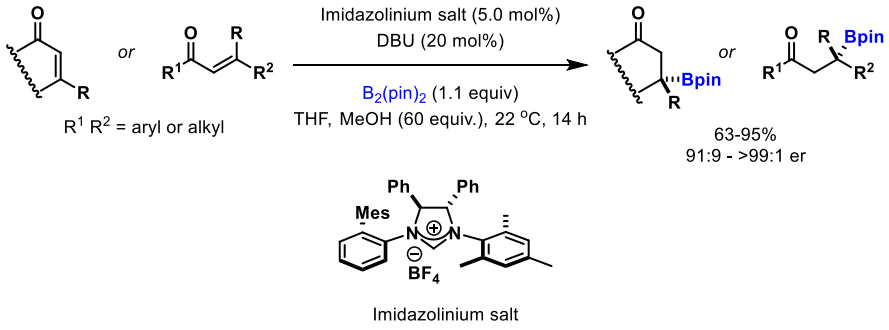


Figure 1.11: Hoveyda's report on metal-free conjugate borylation of acyclic/cyclic enones.[38]

An extension of the conjugate borylation methodology was reported by Wu and Zhang in 2018 to incorporate substrates bearing trifluoromethyl groups in the β-position of vinyl esters and enones.[25] A ferrocene-derived P,N-bidentate ligand (*i.e.*, ^{i}Pr-FOXAP) was used in conjugation with $CuNO_3.5H_2O$ to generate the active borylation catalyst. In the event chiral tertiary boronic esters bearing a trifluoromethyl group at the chiral carbon were formed in excellent yields and high levels of enantioselectivity (Figure 1.12).

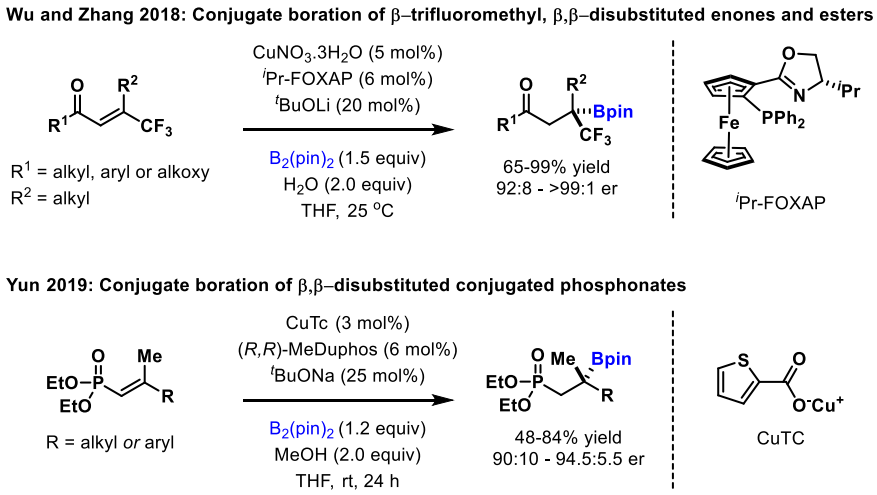


Figure 1.12: A: Conjugate borylation to access quaternary stereocenter bearing a -CF_3 and a boronic ester functionality. B. Conjugate borylation to access phosphonate-functionalized chiral tertiary boronic esters.[24,25]

Recently, Yun reported an yet another extension of this methodology to incorporate vinyl phosphonates, generating β-chiral tertiary boronic esters.[24] Copper thiophene-2-carboxylate was employed as the precatalyst in combination with the chiral bisphosphine bidentate ligand MeDuphos to generate the active catalyst in-situ. The products generated using Yun's methodology are the same products we have initially reported via phosphonate-directed catalytic asymmetric hydroboration of allylic (*i.e.*, β,γ-unsaturated)

phosphonate-substrates and the synthesis of phosphonate-functionalized chiral boronic esters is discussed in length in this dissertation in Chapters 2 and 3.

The third approach to the preparation of chiral tertiary boronic esters, the allylic substitution of trisubstituted allylic carbonates bearing an alkyl or aryl group, was introduced in 2010 by Hoveyda. This approach proves especially useful for the efficient construction of tertiary allyl boronic esters.[26] *Cis*- or *trans*- trisubstituted alkenes were employed and a Cu-NHC complex is used for efficient catalysis. Mechanistically, allylic substitution reactions are similar to conjugate borylation reactions. The initial addition of a nucleophilic boryl species occurs at the more substituted position of the alkene leading to concerted or stepwise loss of the carbonate functionality (Figure 1.13).

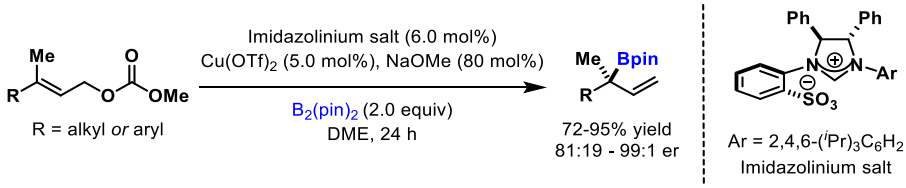


Figure 1.13: Hoveyda's allylic substitution methodology to access chiral tertiary boronic esters.

The fourth approach to the preparation of chiral tertiary boronic esters, catalytic conjunctive cross-coupling reactions, was reported by Morken in 2018.[27] Conjunctive cross-coupling involves three different chemical components: an alkyl or vinyl lithium, a complementary alkyl or vinyl boronic ester and an appropriate aryl halide or pseudo-halide (Figure 1.14). A three-component palladium-catalyzed conjunctive cross-coupling reactions is proposed to occur via a 1,2-metallate shift of vinyl boron-ate complexes in the presence of a palladium or a nickel catalyst. The vinyl boron-ate complex can be prepared

using two different ways: (a) Addition of an alkyl lithium to a vinyl boronic ester, or (b) Addition of a vinyl lithium to an alkyl boronic ester. The oxidative addition complex of a palladium-catalyst with an aryl electrophile undergoes coordination with the alkene in the boron-ate complex which triggers a 1,2-metallate rearrangement resulting in the construction of the chiral tertiary boronic ester. Subsequent reductive elimination of the C-C bond from the Pd-intermediate completes the catalytic cycle.

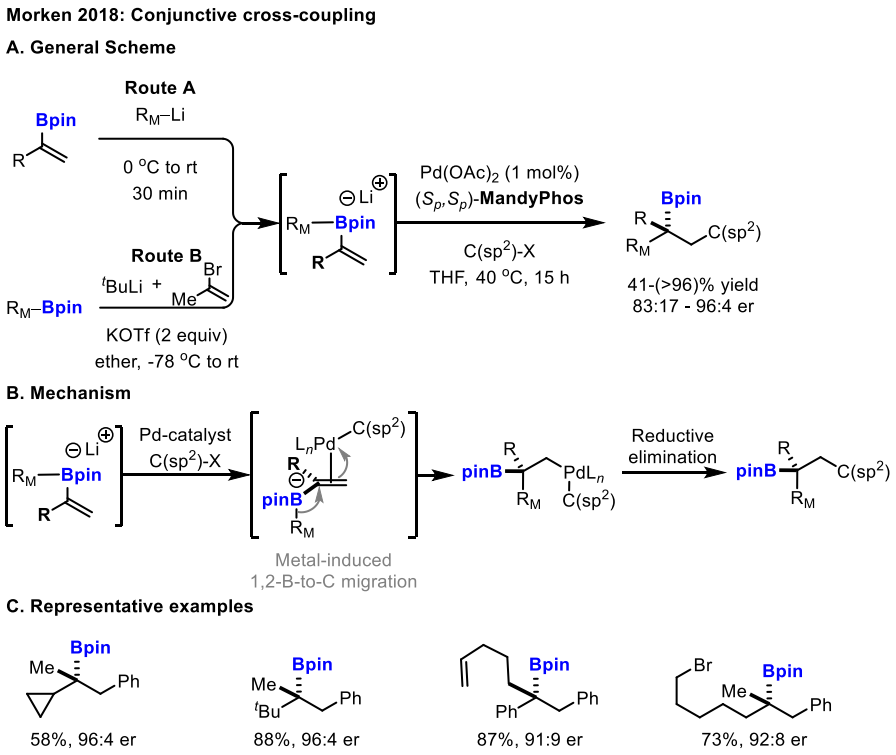


Figure 1.14: Morken's conjunctive cross-coupling methodology to access chiral tertiary boronic esters.[27]

1.3. Overview of the Fifth Approach: Development of Catalytic Asymmetric Hydroboration (CAHB) and it's utility in the synthesis of chiral tertiary boronic esters

In 1956, Dr. B. C. Subba Rao working in the laboratory of Dr. H. C. Brown discovered hydroboration of alkenes. Rao was examining the reducing characteristics of borane by treating sodium borohydride in diglyme in the presence of aluminum chloride and observed the reduction of ethyl oleate under standard conditions. It was soon established that the C=C bond in ethyl oleate was undergoing B-H addition resulting in the formation of the corresponding organoborane.[39] This discovery led to a new era of boron chemistry and soon several groups were interested in the utility of organoboranes and this eventually led to Prof. H. C. Brown receiving the 1979 Nobel Prize in Chemistry jointly with Prof. Georg Wittig for "their development of the use of boron- and phosphorus-containing compounds, respectively, into important reagents in organic synthesis".[40]

The first report of metal-catalyzed hydroboration was reported in 1981 by Wilczynski and Sneddon in which a dicobalthexacarbonyl complex was shown to be effective in catalyzing hydroboration of dimethylacetylene by pentaborane.[41] Subsequently, in 1985, Mannig and Nöth (1985) reported the chemoselective hydroboration of hex-5-en-2-one.[42] The enone was shown to undergo rhodium-catalyzed hydroboration with catecholborane at the alkene but in the absence of a rhodium catalyst, the ketone underwent selective hydroboration. Hayashi (1989) reported the first Rh-catalyzed asymmetric hydroboration of styrenes: the selectivity attained giving 96% ee is among the highest obtained in asymmetric reactions by means of a transition-metal catalyst.[43]

The next three decades or so saw an active development in the field of catalytic asymmetric hydroboration (CAHB) of several different types of substrates leading to new routes to chiral organoboranes.[44] Several initial reports were restricted to simple

monosubstituted styrene derivatives. Building on the work of Evans and coworkers, Takacs and coworkers published in 2008 the first report on the amide-directed CAHB of non-styrenyl disubstituted internal alkenes.[45] From that point onward, the field of CAHB saw a renewed growth with numerous groups around the world contributing to new chemistries. Most importantly, however, the development of catalysts for efficient hydroboration (*i.e.*, boron-hydride addition) of different classes of alkenes effectively resulted in the contruction of chiral primary and secondary boronic esters only.

As discussed earlier in this chapter, chiral tertiary boronic esters are important classes of compounds, but their access via asymmetric hydroboration wasn't reported until recently. In 2015, Tang and workers published the first report to efficiently access α-amino chiral tertiary boronic esters via formal asymmetric hydroboration.[28] α-Aryl enamides were shown to undergo directed hydroboration with bispinacolatodiboron ($B_2(pin)_2$) in the presence of a rhodium-catalyst with BI-DIME as the chiral ligand (Figure 1.15). A single chiral phosphine ligand coordinated to the rhodium precatalyst $Rh(nbd)_2BF_4$ was proposed to be the active hydroboration catalyst. Mechanistically, this transformation was proposed to occur via a tertiary alkyl rhodium intermediate in the catalytic cycle. Oxidative addition of $B_2(pin)_2$ to the Rh(I)-complex leads to the formation of bis-boryl rhodium (III) intermediate which subsequently reacts with the acidic N-H of an enamide substrate to afford boryl rhodium (III) hydride intermediate. Migratory insertion of the alkene C=C bond to the Rh-H bond generates the putative tertiary alkyl-rhodium intermediate and reductive elimination of the C-B bond from this complex forms the tertiary boronic ester product and regenerates the active catalyst. The presence of protic N-H is said to be important in this reaction to generate the Rh-H (rhodium-hydride) in-situ.

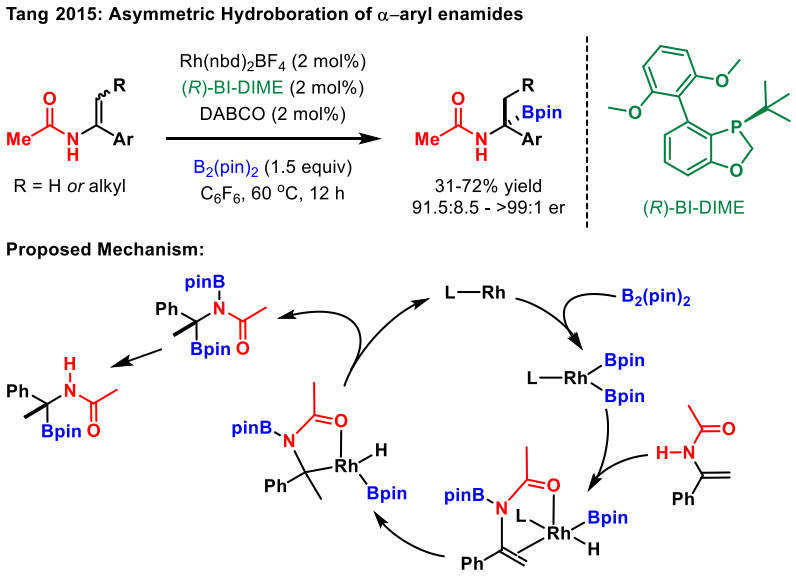


Figure 1.15: Tang's rhodium-catalyzed asymmetric hydroboration of α-aryl enamides and its mechanism.[28]

Shortly after Tang's publication, Takacs and coworkers reported in 2016 the rhodium-catalyzed CAHB of allyl-oxime substrates resulting in a facile entry to chiral all-alkyl tertiary boronic esters (Figure 1.16).[29] A chiral rhodium complex generated in-situ from a commercially available precatalyst, $Rh(nbd)_2BF_4$, in conjugation with a TADDOL-derived chiral cyclic phosphite, was shown to efficiently catalyze hydroboration of alkyl-substituted methylidenes and trisubstituted alkenes with the formation of chiral tertiary boronic esters. The oxime-functionality was important for this reaction as prior work on the corresponding amide-directed reactions afforded boration at the less substituted terminus of the alkene. The oxime-directed reactions were shown to be highly site- and regioselective; the presence of multiple alkenes could be accommodated with the alkene proximal to the directing group undergoing preferential reaction. Furthermore, the reactions were also shown to be highly diastereoselective in case of chiral substrates.

Depending on the choice of the chiral catalyst used, either diastereomer of the product from a given chiral substrate could be prepared.

In 2019 Bochat, Shoba and Takacs reported a regiodivergent enantioselective oxime-directed CAHB of aryl-substituted methylidenes to access regioisomeric chiral primary and tertiary boronic ester products.[30] Simple changes in the TADDOL-ligand were shown to effect regiodivergent behavior under the standard reaction conditions. In this work, chiral tertiary benzylic boronic esters were generated from the corresponding vinyl arene substrates. At the same time, the work described in Chapters 2-5 of this dissertation were also in progress (*vide infra*).

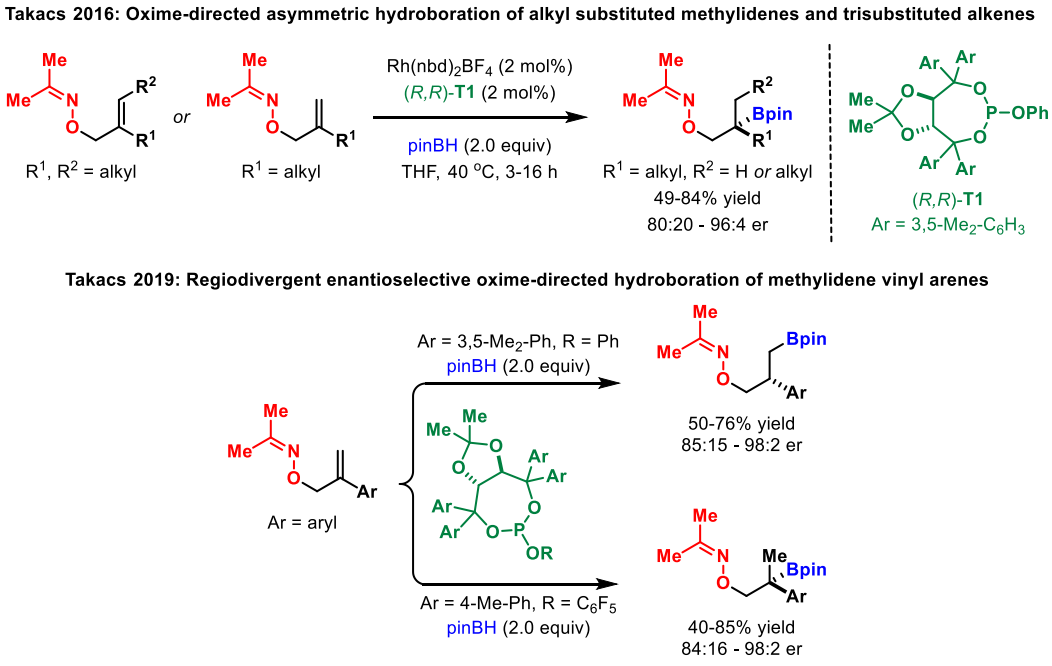


Figure 1.16: Takacs' oxime-directed catalytic asymmetric hydroboration (Adapted with permission from Ref. 30. Copyright 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim).[20,30]

1.4. Stereospecific transformations of chiral tertiary boronic esters

As discussed earlier in this chapter, the development of methods for the enantioselective synthesis of chiral tertiary boronic esters has received considerable attention over the past decade. Section 1.2 and 1.3 of this chapter summarized the different catalytic methods available for the enantioselective construction of chiral tertiary boronic esters. Alongside the development of methods for efficient synthesis of chiral tertiary boronic esters, significant research has been also devoted to the development of methods for their stereospecific functionalization to prepare other useful molecules. This section reviews the transformations that are currently available for stereospecific functionalization of chiral tertiary boronic esters.

Chiral tertiary alcohols are important molecules in medicinal chemistry. The presence of a tertiary alcohol functionality adds polarity to a molecule and hence increases water solubility. Moreover, the steric hindrance around the tertiary alcohol functionality makes them essentially non-nucleophilic and non-oxidizable; hence, non-reactive in biological systems. The stereospecific oxidation of a chiral tertiary boronic ester efficiently yields the corresponding alcohol. Common oxidation conditions often employed are a combination of H_2O_2 and NaOH, generating the hydroperoxide anion in-situ, or use of $NaBO_3.4H_2O$; the latter is considered to be milder oxidation conditions. The mechanism of oxidation involves formation of the boron-ate complex with the hydroperoxide anion which undergoes a 1,2-migration to form the C-O bond and the subsequent hydrolysis of the O-B to an O-H bond completes the reaction (Figure 1.17). Oxidation of chiral tertiary boronic esters to the corresponding chiral tertiary alcohols is perhaps the most widely used

transformation and generally occurs with complete retention of configuration at the migrating carbon.

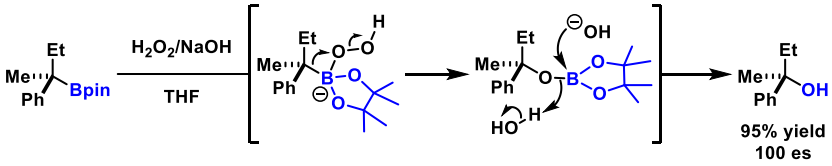


Figure 1.17: Oxidation of chiral tertiary boronic esters to form chiral tertiary alcohols.

Chiral tertiary amines have found important applications in asymmetric catalysis either as chiral bases for enantioselective deprotonation reactions or for forming diastereomeric complexes for resolving mixtures of chiral acids.[46] Chiral amines are also highly prevalent in several bioactive molecules including many pharmaceutical drugs and drug candidates. The first report of converting chiral tertiary boronic esters into chiral tertiary carbinamines via stereospecific C-B to C-N transformation was reported by Aggarwal and co-workers in 2011 (Figure 1.18).[47] In Aggarwal's methodology, a chiral tertiary boronic ester was first transformed into a chiral tertiary trifluoroborate salt. The salt reacts with $SiCl_4$ to generate the highly electrophilic alkyl dichloroborane in-situ. Subsequent reaction with an alkyl-azide forms the boron-ate complex which undergoes facile 1,2-B-to-N migration; aqueous workup generally affords the chiral tertiary carbinamine in excellent yield with high levels of stereoretention. Generation of the chiral dichloro-organoborane intermediate is required because boronic esters are not electrophilic enough to undergo ate-complex formation with alkyl azides. This reaction has been carried out in an intramolecular fashion and can be applied to non-benzylic chiral tertiary boronic esters as well. However, the utility of this transformation can be limited by the harsh conditions required.

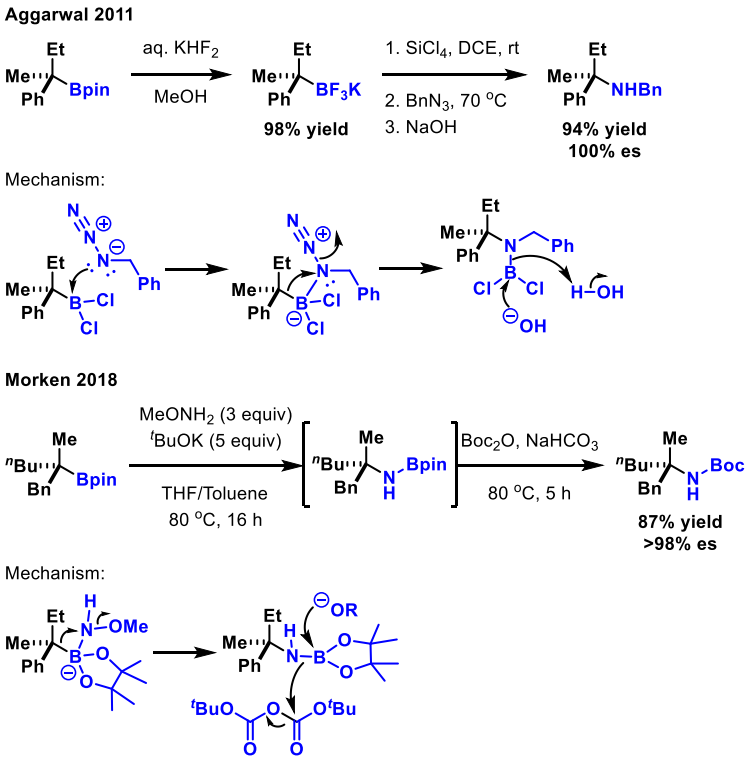


Figure 1.18: Amination of chiral tertiary boronic esters to form chiral tertiary carbinamines.

Morken reported in 2018 a direct stereospecific transformation of chiral boronic esters to carbinamines via treatment with methoxyamine and potassium tert-butoxide (Figure 1.18).[48] Mechanistically, methoxyamine is proposed to add to a tertiary boronic ester to form a boron-ate complex and the potassium tert-butoxide deprotonates the amination reagent once the nitrogen is acidified via coordination to the boron center. The boron-ate complex then undergoes 1,2-B-to-N migration with the loss of methoxide with subsequent workup to form the tertiary carbinamines. A few challenging substrates including a chiral tertiary boronic ester bearing tertiary substituent such as an isopropyl group can be efficiently converted to the corresponding amine using this methodology. The major limitation of this methodology is the formation of high degree of non-stereospecific

protodeboronation side products which are obtained with chiral tertiary benzylic boronic esters.

Stereospecific C-B to C-H (or C-D) bond substitution can be used with chiral tertiary boronic esters to enable facile access to chiral tertiary stereogenic centers.[49] Aggarwal's group showed that bis-benzylic boronic esters undergo protodeboronation using CsF and H_2O in dioxane at 30 °C (Figure 1.19). Mechanistically, the TBAF.3H_2O mediated protodeboronation reaction is proposed to occur via a hydrogen-bonded boron-ate intermediate which delivers the proton from the same side as that of the boron atom. The main driving force for this transformation is the formation of stronger B-F bonds. Monoaryl tertiary boronic esters required more activated conditions for protodeboronation, however, TBAF.3H_2O has been used for their efficient protodeboronation. Unfortunately, non-benzylic boronic esters have thus far not been found to efficiently undergo protodeboronation in the presence of a F^- source; forcing conditions instead lead to homolytic cleavage of the C-B bond and loss of stereochemistry.

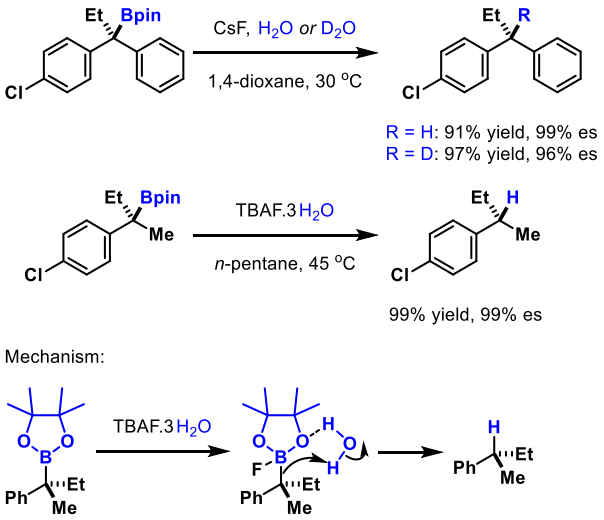


Figure 1.19: Stereospecific proto/deutero-deboronation of chiral tertiary boronic esters.

Zweifel and coworkers reported the formation of a single alkene isomer from a borane starting material via addition of iodine to alkenyl dialkylborane in 1967.[50] Building upon Zweifel's work, Aggarwal investigated the use of iodine promoted 1,2-migration to achieve stereoselective synthesis of chiral centers attached to alkenes. Upon subjecting chiral tertiary boronic esters to Zweifel's olefination conditions, Aggarwal's group found that vinylmagnesium bromide adds three times to the boronic ester to form the corresponding boron-ate complex. Subsequent treatment of this boron-ate intermediate with I_2 and MeONa/MeOH results in the overall substitution of the boronic ester with a vinyl group (Figure 1.20).[51]

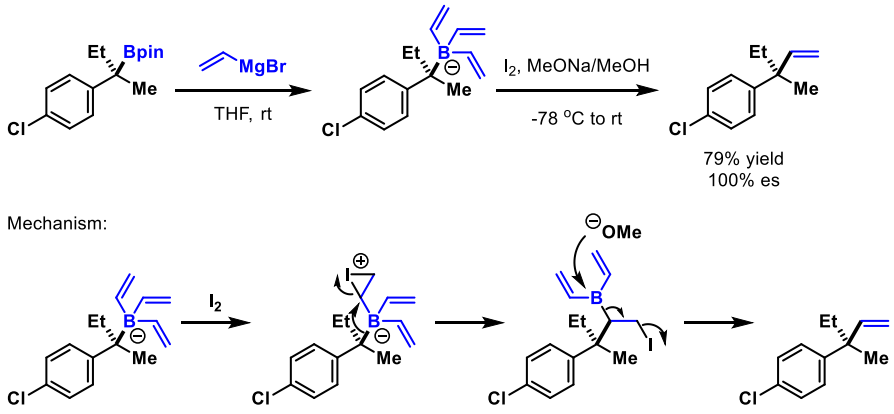


Figure 1.20: Stereospecific vinylation of chiral tertiary boronic esters.

An extension of the vinylation conditions described above was reported for the transformation of a chiral tertiary boronic ester into the corresponding methyl-ketone (Figure 1.21).[52] In this transformation, ethoxyvinyl lithium (generated via treatment of ethyl-vinyl ether with ^{t}BuLi) adds to the boronic ester to form a boron-ate complex which upon subsequent treatment of I_2 forms the iodonium ion intermediate facilitating the 1,2-metallate rearrangement. Subsequent treatment with MeONa and MeOH leads to the

overall substitution of the tertiary boronic ester to the ethoxy-vinyl intermediate. Subsequent hydrolysis of the ethyl-vinyl ether leads to the formation of the methyl ketone.

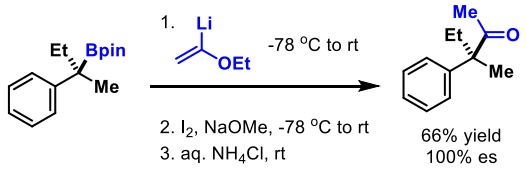


Figure 1.21: Stereospecific transformation of chiral tertiary boronic esters to methyl ketones.

Direct extension of the olefination protocol for stereospecific transformation of chiral boronic esters to alkynes is challenging. The challenge results in part due to the reversible reaction of the lithiated alkyne with the boronic ester. Under such circumstances, competing addition of a subsequently added electrophile (*e.g.*, I_2) results in addition of the iodine across the alkyne instead of inducing the desired 1,2-metallate rearrangement.[53] The Aggarwal group reported a two-step protocol for the stereospecific transformation of a chiral tertiary boronic ester into an alkyne functionality via the following sequence: stereospecific olefination with a lithiated vinyl carbamate followed by subsequent 1,2-elimination from the intermediate using *tert*-butyl lithium to afford the alkene product (Figure 1.22).[54] Their reported stereospecific alkynylation of chiral tertiary boronic esters is highly efficient; products can be obtained in excellent yields and with essentially complete enantiospecificity.

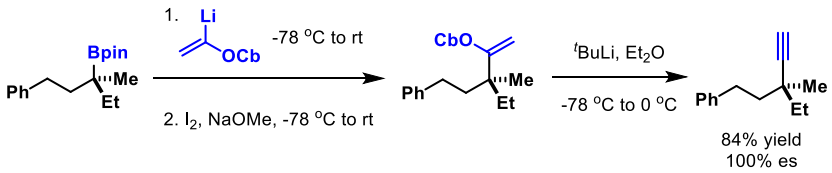


Figure 1.22: Stereospecific alkynylation of chiral tertiary boronic esters.

Homologation of a chiral tertiary boronic ester by one or more carbon units allow facile chain extension while retaining the boronic ester functionality for further reactions. The Aggarwal group developed several procedures for stereospecific homologation of chiral tertiary boronic esters (Figure 1.23).[52] Treatment of a chiral tertiary boronic ester with dichloromethyl lithium followed by oxidation is frequently used to transform a boronic ester to an aldehyde functionality (Figure 1.23A).[52] A similar reaction with bromomethyl lithium leads to the homologation to a boronic ester extended by one carbon atom. The product after homologation is a quaternary all-carbon stereocenter bearing a primary boronic ester unit (Figure 1.23B).[52]

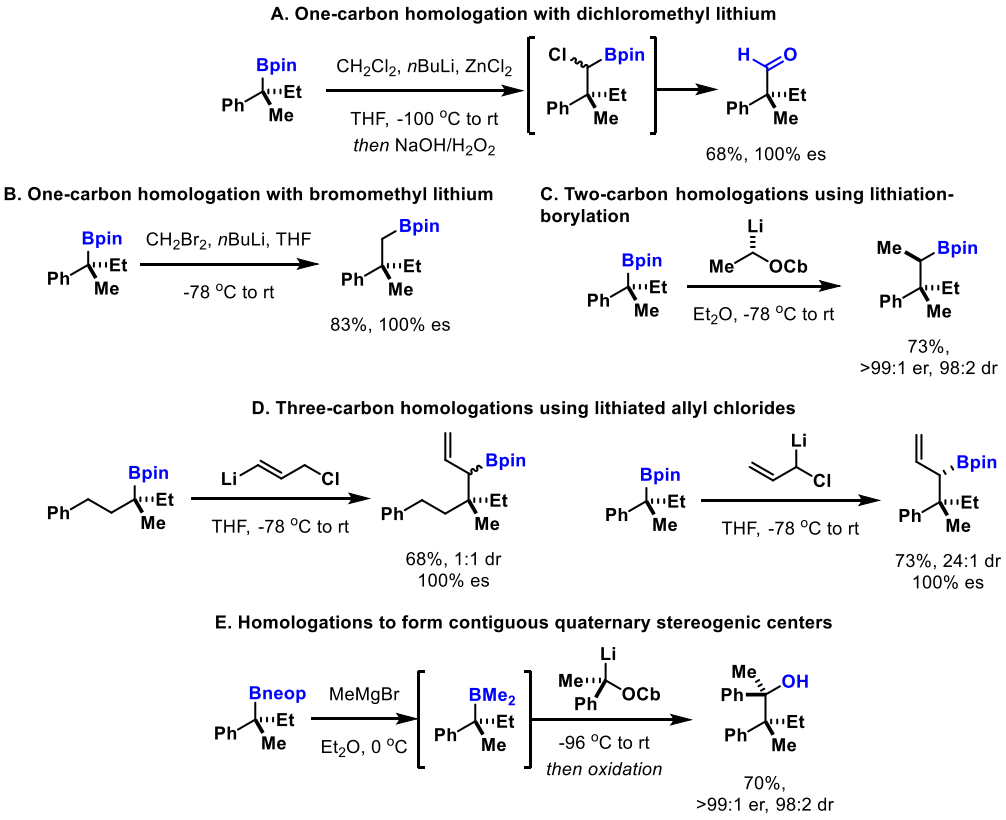


Figure 1.23: Homologation reactions of chiral tertiary boronic esters

Aggarwal's group a developed two-carbon homologations using chiral lithiated reagents to form a new chiral secondary boronic ester with two contiguous chiral centers in one molecule (Figure 1.23C).[55] The homologation methodology has been extended for three-carbon homologations using lithiated allyl chlorides.[56] The secondary allyl-boronic ester products are formed in excellent yields and enantiospecificity (Figure 1.23D). These methodologies have been extended to the synthesis of molecules bearing contiguous quaternary carbon stereocenters as well (Figure 1.23E).[57] Although the 1,2-B-to-C migration did not occur with the tertiary boronic ester, the reaction proceeds with the mixed borane (derived after treatment of the neopentyl glycol boronic ester with methyl magnesium bromide) to afford the tertiary alcohol after oxidation.

Cross-couplings reactions of chiral tertiary boronic esters have also received significant attention in recent years. Several of these methods lead to the formation of quaternary carbon stereocenters. Chiral tertiary trifluoroborate salts undergo facile addition reactions with electron-deficient aldehydes (*e.g.* 4-nitrobenzaldehyde) in the presence of $[Rh(cod)Cl]_2$ through a stereoretentive pathway.[58] The retention of configuration is explained by assuming rhodium acting as a Lewis-acid to simultaneously coordinate both the aldehyde and the boronic ester and facilitate the C-C bond formation (Figure 1.24). Initial addition leads to the formation of a 1:1 mixture of the secondary alcohol product, oxidation of which generates the aryl ketone in excellent yield and high degree of enantiospecificity.

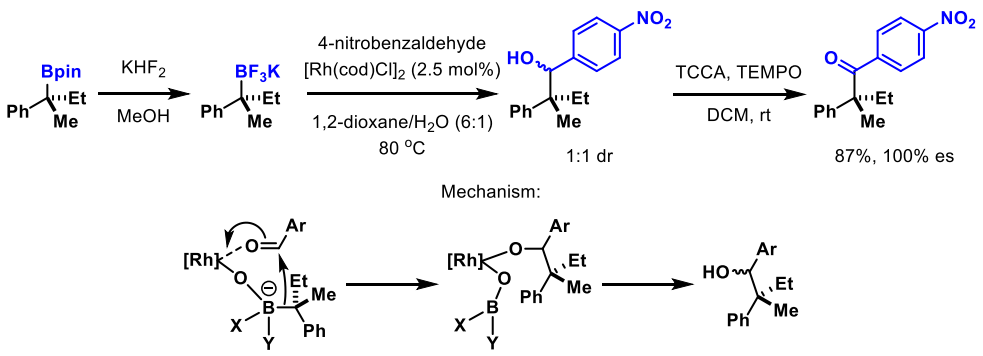


Figure 1.24: Stereospecific addition of tertiary trifluoroborate salts to aldehydes

---

In 2014, Aggarwal published the transition metal-free cross-coupling of chiral tertiary boronic esters with electron-rich 5- and 6-membered aromatic rings (Figure 1.25).[3] Mechanistically, a lithiated aromatic ring (generated via lithium-halogen exchange or via C-H lithiation) is added to a chiral tertiary boronic ester to form the corresponding boron-ate complex. The latter subsequently undergoes electrophilic aromatic substitution (EAS) with an appropriate electrophile to generate a stabilized cation. The cation then triggers the 1,2-B-to-C migration and after elimination gives the corresponding cross-coupled product. This transformation can be carried out using 5-membered or 6-membered electron-rich aromatic rings in excellent yields and enantiospecificity, but thus far has been limited to electron rich aromatics.

Modifications of the Aggarwal transition metal-free cross-coupling methodology continue to expand its scope for certain desirable cross-coupling partners. For example, coupling with common nitrogen heterocycles (*e.g.* pyridines) was recently been shown to be possible. An initial boron-ate-complex is formed by the addition of lithiated pyridines. Acylation of the nitrogen using Troc-Cl then facilitates the 1,2-metallate rearrangement.[59]

Oxidation of the resulting boronic ester enables rearomatization affording the coupled product (Figure 1.26A).

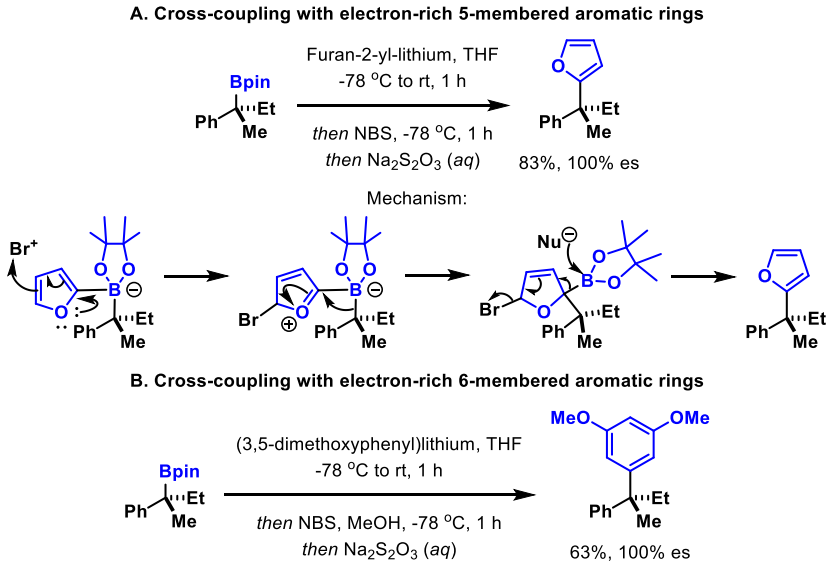


Figure 1.25: Stereospecific coupling of chiral tertiary boronic esters with 5- and 6-membered electron rich aromatic rings.

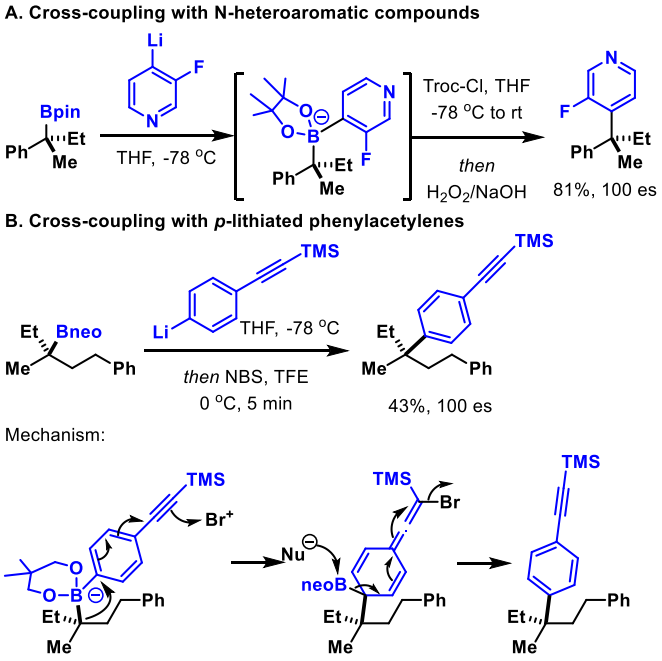


Figure 1.26: Stereospecific coupling of chiral tertiary boronic esters with N-heteroaromatic compounds and with phenyl acetylenes.

A conceptually similar approach was developed for the cross-coupling with lithiated phenylacetylenes.[60] In this transformation, the alkyne functionality of the intermediate boron-ate complex reacts with NBS (similar to the strategy used for electron rich aromatics) triggering the 1,2-migration to form a dearomatized bromoallene intermediate. With neopentyl glycol-derived boronic esters, subsequent elimination and rearomatization occurs giving rise to the cross-coupled products. With pinacol-boronates, however, the boron migrates to the adjacent carbon resulting in the formation of *ortho*-boron incorporated products.

Very recently Aggarwal's group published reports on stereospecific cross-couplings of chiral tertiary boronic esters with dilithio-phenolate species and lithiated aryl hydrazines for stereospecific transformation of a boronic ester to a phenol or aniline functionality (Figure 1.27).[61,62] In case of the cross-coupling with a dilithiophenolates, a tertiary boronic ester after undergoing ate-complex formation undergoes reaction with Martin's sulfurane or Ph_3BiF_2 which triggers the 1,2-B-to-C migration resulting in the formation of the cross-coupled products with high levels of stereospecificity.[61] In a conceptually similar transformation with lithiated aryl hydrazines, the intermediate boron-ate complex undergoes acylation at the terminal nitrogen which triggers a N-N bond cleavage along with a 1,2-metallate rearrangement.[62] Subsequent workup results in the cross-coupled aniline product.

This section summarized the stereospecific transformations known for chiral tertiary boronic esters in the present literature (as of June 2019). Several of these stereospecific transformations are based on variations of the original Matteson's 1,2-metallate rearrangement. Efficient utility of the latter has been used on a variety of contexts

particularly for the stereospecific cross-coupling reactions with chiral tertiary boronic esters. As stereospecific transformations continue to evolve, the subsequent synthetic utility of chiral tertiary boronic esters is on the rise.

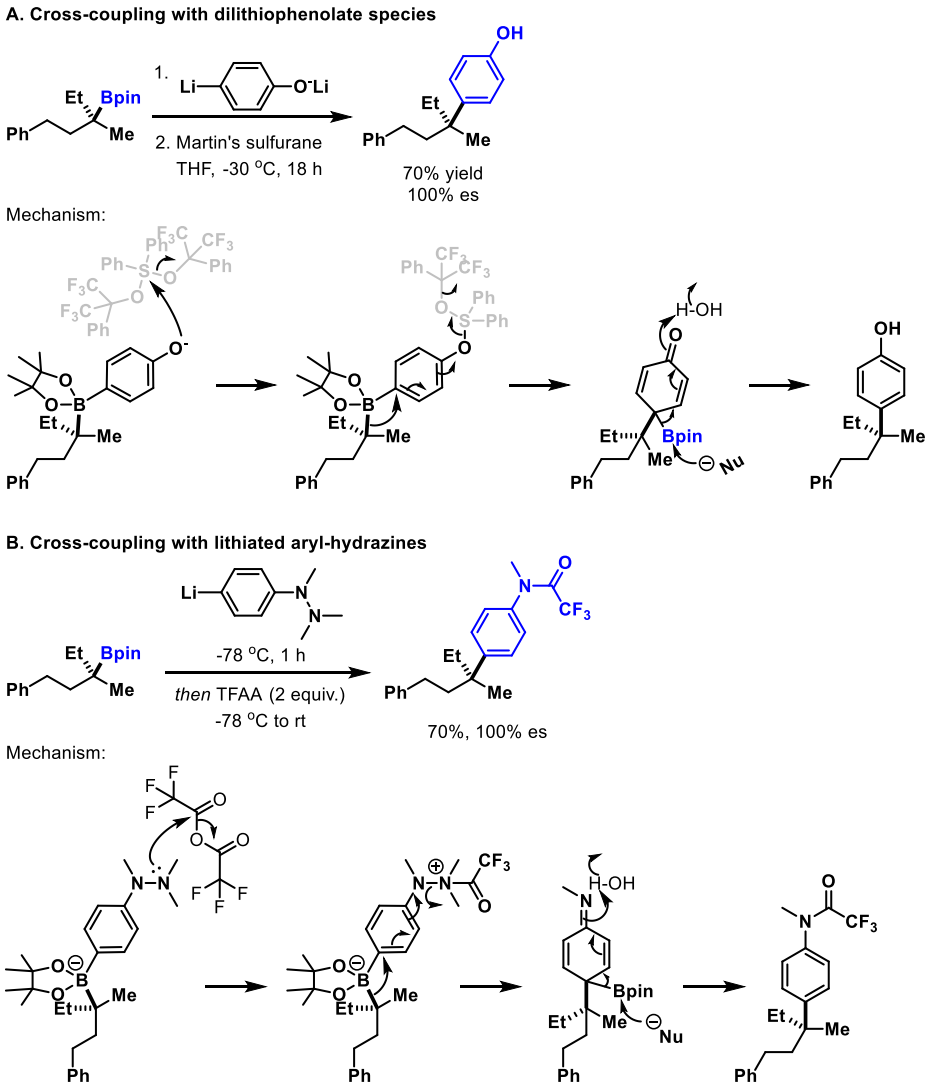


Figure 1.27: Stereospecific coupling of chiral tertiary boronic esters with dilithio-phenolates and lithiated aryl hydrazines to phenols or anilines.

1.5. Introduction to the phosphonate-functionality: biological relevance and directing properties

Phosphonates and their corresponding phosphonic acids are organophosphorus compounds containing a C-P$(OR)_2$ in which R can be alkyl, aryl or H. These closely approximate the structures of the corresponding phosphates, yet include a hydrolysis resistant C-P linkage.[63]

Figure 1.28 shows the selected examples of important bioactive phosphonates or phosphonic acids of high relevance in human health and in agriculture. Fosfomycin (Monurol) is a broad spectrum antibiotic that concentrates in kidney and bladder and is used to treated urinary tract infections. It was initially isolated from the broth cultures of *Streptomyces fradiae* in 1969, however, it is presently accessed predominantly via chemical synthesis. Glyphosate (*N*-phosphonomethylglycine) is a broad spectrum herbicide and a crop desiccant which was brought into market for agricultural use in 1974 by Monsanto under the trade name Roundup. Zoledornate and phosphonoformate (Foscarnet) are analogs of pyrophosphate and are used to treat osteroporosis and herpes, respectively. Zoledornate also exhibits anticancer activity. Perzinfotel is an analog of N-methyl-D-aspartate (NMDA) and thus acts as an antagonist towards NMDA receptors. Tenofivir is sold under the drug name Viread and is marketed by the biotech company Gilead Sciences and was approved by the U.S. FDA for treatment of HIV on October 26, 2001 and on August 11, 2008 for chronic hepatitis B.[64] Upon dephosphorylation in the cell, Tenofovir acts as an inhibitor of viral reverse transcriptase by mimicking deoxynucleotide triphosphates. It is listed by the World Health Organization (WHO) as an essential medication for the treatment of HIV and Hepatitis B.

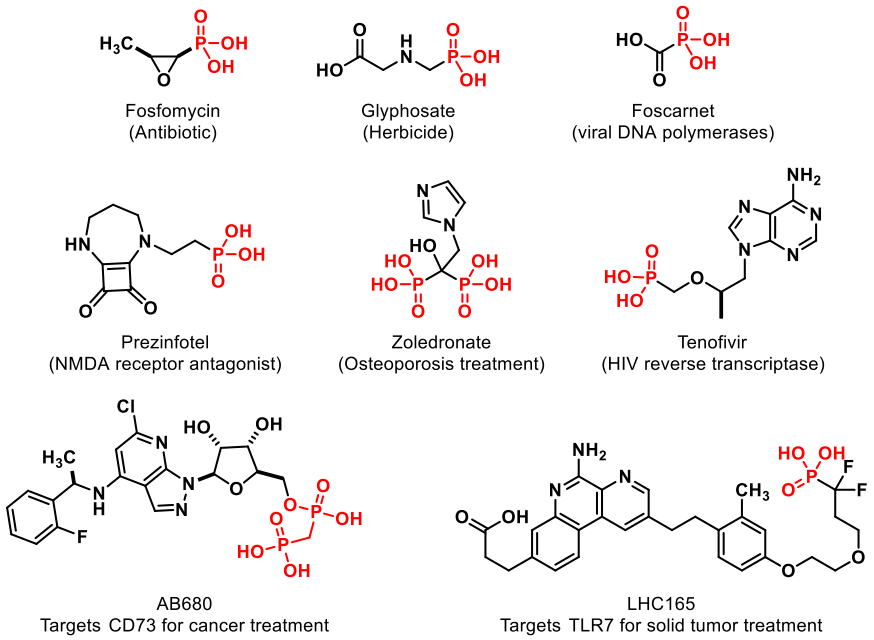


Figure 1.28: Selected examples of bioactive phosphonates

The 2019 ACS National meeting in Orlando FL had a session named "First-time Disclosure of Clinical Candidates" by the Division of Medicinal Chemistry which showed glimpses of drug-candidate structures not previously made public.[65] C&EN made a cover story on this topic; two of the eight structures made public at ACS Orlando contained phosphonic acid functionality. AB680 is a derivative of methylene diphosphonic acid is a checkpoint inhibitor developed by Arcus Biosciences for the treatment of cancer. Checkpoint inhibitors successfully disrupt the binding interaction between a protein and a checkpoint protein that stops immune T-cells from killing cancer cells. This results in checkpoint inhibitors turning immune cells loose to attack tumor cells. LHC165 features a difluorophosphonate and it has been developed by Novartis Research Foundation for the treatment of solid tumors. LHC165 is developed as a vaccine adjuvant, molecules that switch on the immune system to enhance a vaccine's effect. It activates toll-like receptor

(TLR7) and triggers the release of infection-clearing proteins. It was subsequently tested for its effectiveness in immuno-oncology.

In organic synthesis, phosphonates are routinely employed as components of Horner-Wadsworth-Emmons olefination for the synthesis of stereodefined alkenes (Figure 1.29A). In addition, although used less frequently, thiophosphonates can also be used for carrying out olefination.[66] While β-hydroxyphosphonates are stable isolable molecules, the corresponding β-hydroxy thiophosphonates readily undergo elimination to afford alkenes (Figure 1.29B) . Yet another common utility of the phosphonate-functionality is in the context of active esters in α-oxophosphonates.[67] Acylphosphonates are considered analogs of acid chlorides and active esters. These are excellent electrophiles that react with a variety of nucleophiles resulting in the formation of various substitution products. For example, substitution reactions with alcohols and amines with α-oxophosphonates result in formation of esters and amides (Figure 1.29C). These are some of the key reactions that will be discussed later in this dissertation.

Recently, phosphonates have been elegantly utilized as directing groups in aryl C-H functionalization reactions (Figure 1.30). For example, Kim and others have explored the utility of benzylic phosphonic monoesters for the selective ortho C-H functionalizations using a Pd(II)-catalyst (Figure 1.29A). The directing group positions the metal to the ortho-position and subsequently a Heck-type reaction leads to the formation of a C-C bond. A similar transformation has also been reported with aryl phosphonates in a rhodium-catalyzed reaction (Figure 1.29B).[68,69] Maiti and coworkers developed meta C-H functionalization reactions using a cyanophenol-based directing group linked with a benzyl phosphonate (Figure 1.29C).[70] The reaction is proposed to go through a 11-membered

palladacycle stabilized by the cyanide functionality. Subsequent reductive elimination and C-C bond formation results in the meta C-H functionalization of such systems.

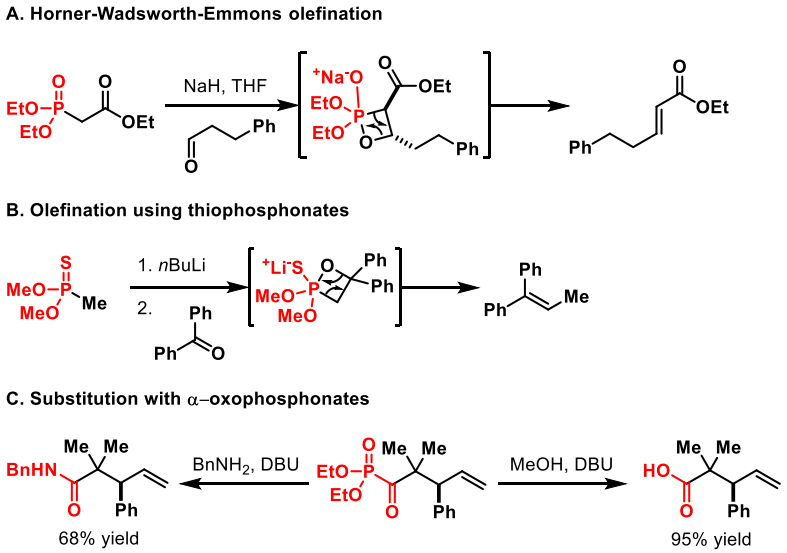


Figure 1.29: Utility of the phosphonate-functionality in organic synthesis.

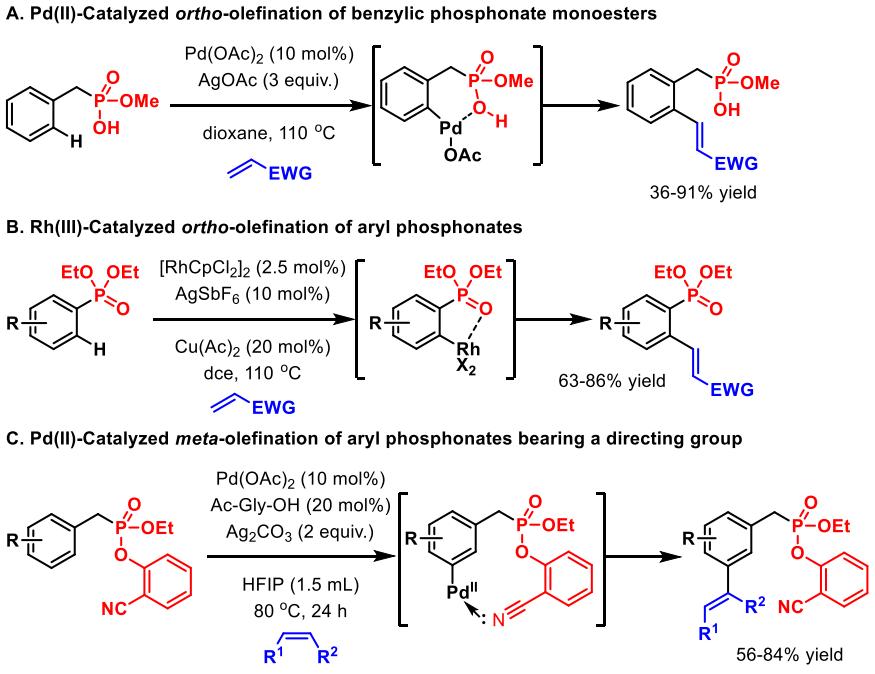


Figure 1.30: Phosphonate-directed aryl C-H functionalizations.

As discussed briefly above, the Takacs research group is actively engaged in preparing multifunctional chiral boronic esters via rhodium-catalyzed, directed catalytic asymmetric hydroboration (CAHB) of functionalized alkene substrates capable of two-point binding (*i.e.*, chelation). For example, efficient amide directed CAHB resulted in the highly selective synthesis of chiral β-,γ- and δ-borated amide derivatives. Replacing the amide-functionality with an oxime-directing group led to the unprecedented, ligand-controlled regiodivergent access to chiral boronic esters by CAHB.

Encouraged by the success of the amide- and oxime-directing groups, and the literature precedents set by other groups for the efficient utility of phosphonates as directing groups for novel modes of C-H activation, we set out to explore the potential effectiveness of the phosphonate-functionality as a directing group in CAHB. We envisioned that a successful phosphonate directed CAHB would result in access to a new class of chiral molecules, chiral borylated phosphonates, which would enable new possibilities as chiral synthons. We further imagined that chiral borated phosphonates would be easily converted to chiral hydroxyphosphonates. Hydroxyphosphonates are known in drug candidates and enzyme inhibitors and in particular, β-hydroxyphosphonates mimic the corresponding β-hydroxy carboxylic acids and amino acids.[71] Our research into phosphonate-directed CAHB, as well as the chemistry of the functionalized phosphonate products will be discussed in Chapters 2-4.

1.6. Summary

In summary, this chapter covered a brief introduction to chiral boronic esters: their synthetic, biological and medicinal relevance. In addition, this chapter entailed a

comprehensive coverage of the reported methods of enantioselective synthesis of chiral tertiary boronic esters and their stereospecific transformations known in the literature to date (June 2019). Several of these stereospecific transformations are based on the Matteson's 1,2-metallate rearrangement. Efficient utility of the latter has been used on a variety of contexts particularly for the stereospecific cross-coupling reactions with chiral tertiary boronic esters. An introduction to the phosphonate functionality highlighting their biological relevance and directing properties, and the initial goals behind the development of phosphonate-directed catalytic asymmetric hydroboration were covered in this chapter as well.

1.7. References

(1) For leading examples, see (a) Wu, J.; Lorenzo, P.; Zhong, S.; Ali, M.; Butts, C. P.; Myers, E. L.; Aggarwal, V. K. "Synergy of synthesis, computation and NMR reveals correct baulamycin structures" *Nature* **2017**, *547*, 436. (b) Collins, B. S. L.; Wilson, C. M.; Myers, E. L.; Aggarwal, V. K. "Asymmetric Synthesis of Secondary and Tertiary Boronic Esters" *Angew. Chem., Int. Ed.,* **2017**, *56*, 11700. (c) Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. "A general, modular method for the catalytic asymmetric synthesis of alkylboronate esters" *Science* **2016**, *354*, 1265. (d) Crudden, C. M.; Ziebenhaus, C.; Rygus, J. P. G.; Ghozati, K.; Unsworth, P. J.; Nambo, M.; Voth, S.; Hutchinson, M.; Laberge, V. S.; Maekawa, Y.; Imao, D. "Iterative protecting group-free cross-coupling leading to chiral multiply arylated structures" *Nat. Commun.,* **2016**, *7*, 11065. (e) Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. "Synthesis

of Enantiomerically Enriched Triarylmethanes by Enantiospecific Suzuki–Miyaura Cross-Coupling Reactions" *J. Am. Chem. Soc.*, **2014**, *136*, 5828.

(2) Sandford, C.; Aggarwal, V. K. "Stereospecific functionalizations and transformations of secondary and tertiary boronic esters" *Chem. Commun.*, **2017**, *53*, 5481.

(3) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. " Enantiospecific sp^2–sp^3 coupling of secondary and tertiary boronic esters" *Nat. Chem.*, **2014**, *6*, 584.

(4) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. " Assembly-line synthesis of organic molecules with tailored shapes" *Nature* **2014**, *513*, 10226.

(5) Balieu, S.; Hallett, G. E.; Burns, M.; Bootwicha, T.; Studley, J.; Aggarwal, V. K. "Toward Ideality: The Synthesis of (+)-Kalkitoxin and (+)-Hydroxyphthioceranic Acid by Assembly-Line Synthesis" *J. Am. Chem. Soc.*, **2015**, *17*, 504.

(6) Meng, F.; McGrath, K. P.; Hoveyda, A. H. "Multifunctional organoboron compounds for scalable natural product synthesis" *Nature* **2014**, *513*, 367.

(7) Kan, S. B. J.; Huang, X.; Gumulya, Y.; Chen, K.; Arnold, F. H. "Genetically programmed chiral organoborane synthesis" *Nature*, **2017**, *552*, 132.

(8) Dembitsky, V. M.; Quntar, A. A. A. A.; Srebnik, M. "Natural and Synthetic Small Boron-Containing Molecules as Potential Inhibitors of Bacterial and Fungal Quorum Sensing" *Chem. Rev.*, **2011**, *111*, 209.

(9) Hütter, R.; Keller-Schierlein, W.; Knüsel, F.; Prelog, V.; Rodgers G. C. Jr.; Suter, P.; Vogel, G.; Voser W.; Zähner, H. "The metabolic products of microorganisms. Boromycin" *Helv. Chim. Acta*., **1967**, *50*, 1533.

(10) Kohno, J.; Kawahata, T.; Otake, T.; Morimoto, M.; Mori, H.; Ueba, N.; Nishio, M.; Kinumaki, A.; Komatsubara, S.; Kawashima, K. "Boromycin, an Anti-HIV Antibiotic". *Biosci Biotechnol Biochem.,* **1996**, *60*, 1036.

(11) Hemscheidt, T.; Puglisi, M. P.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Rios, J. L.; Clardy, J. "Structure and biosynthesis of borophycin, a new boeseken complex of boric acid from a marine strain of the blue-green alga Nostoc linckia" *J. Org. Chem.*, **1994**, *59*, 3467.

(12) Kayeka, H.; Takahashi, I.; Okada, G.; Isono, K.; Osada, H. "Epolactaene, a novel neuritogenic compound in human neuroblastoma cells, produced by a marine fungus." *J. Antibiot (Tokyo)* **1995**, *48*, 733.

(13) Xavier, K. B.; Bassler, B. L. "Interference with AI-2-Mediated Bacterial Cell-Cell Communication" *Nature* **2005**, *437*, 750.

(14) Das, B. C.; Thapan, P.; Karki, R.; Schinke, C.; Das, S.; Kambhampati, S.; Banerjee, S. K.; Veldhuizen, P.V.; Verma, A.; Weiss, L. M.; Evans, T. "Boron chemicals in diagnosis and therapeutics" *Future Med Chem.,* **2013**, *5*, 653.

(15) Field-Smith, A.; Morgan, G. J.; Davies, F. E. "Bortezomib (Velcadetrade mark) in the Treatment of Multiple Myeloma" *Ther. Clin. Risk. Manag.* **2006**, *2*, 271.

(16) Sharma, N.; Sharma, D. "An upcoming drug for onychomycosis: Tavaborole" *J. Pharmacol. Pharmacother.*, **2015**, *6*, 236.

(17) Bueschleb, M.; Dorich, S.; Hanessian, S.; Tao, D.; Schenthal, K. B.; Overman, L. E. "Synthetic Strategies toward Natural Products Containing Contiguous Stereogenic Quaternary Carbon Atoms" *Angew. Chem., Int. Ed.* **2016**, *55*, 4156 and references cited.

(18) Matteson, D. S.; Hurst, G. D. "Asymmetric Synthesis of Tertiary Alcohols from α-Halo Boronic Esters" *Heteroat. Chem.*, **1990**, *1*, 65.

(19) Collins, B. S. L.; Wilson, C. M.; Myers, E. L.; Aggarwal, V. K. "Asymmetric Synthesis of Secondary and Tertiary Boronic Esters" *Angew. Chem., Int. Ed.* **2017**, *56*, 11700.

(20) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. "Enantiodivergent conversion of chiral secondary alcohols into tertiary alcohols" *Nature* **2008**, *456*, 778.

(21) Chen, I-H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. "Catalytic Asymmetric Synthesis of Chiral Tertiary Organoboronic Esters through Conjugate Boration of β-Substituted Cyclic Enones" *J. Am. Chem. Soc.*, **2009**, *131*, 11664.

(22) O'Brien, Lee, K.-S.; Hoveyda, A. H. "Enantioselective Synthesis of Boron-Substituted Quaternary Carbons by NHC−Cu-Catalyzed Boronate Conjugate Additions to Unsaturated Carboxylic Esters, Ketones, or Thioesters" *J. Am. Chem. Soc.*, **2010**, *132*, 10630.

(23) Feng, X.; Yun, J. "Conjugate Boration of β,β-Disubstituted Unsaturated Esters: Asymmetric Synthesis of Functionalized Chiral Tertiary Organoboronic Esters" *Chem. Eur. J.*, **2010**, *16*, 13609.

(24) Kim, J.; Lee, H.; Yun, J. "Asymmetric synthesis of chiral tertiary borylated phosphonates bycopper-catalyzed conjugate borylation" *Tetrahedron* **2019**, *32*, 4250.

(25) Liu, B.; Wu, H.-H.; Zhang, J. "Cu(II)-Catalyzed Enantioselective β-Boration of β-Trifluoromethyl, β,β-Disubstituted Enones and Esters: Construction of a CF_3- and Boron-Containing Quaternary Stereocenter" *ACS Catal.*, **2018**, *8*, 8318.

(26) Guzman-Martinez, A.; Hoveyda, A. H. "Enantioselective Synthesis of Allylboronates Bearing a Tertiary or Quaternary B-Substituted Stereogenic Carbon by NHC-Cu-Catalyzed Substitution Reactions" *J. Am. Chem. Soc.,* **2010**, *132*, 10634.

(27) Myhill, J. A.; Zhang, L.; Lovinger, G. J.; Morken, J. P. "Enantioselective Construction of Tertiary Boronic Esters by Conjunctive Cross-Coupling" *Angew. Chem., Int. Ed.*, **2018**, *57*, 12799.

(28) Hu, N.; Zhao, G.; Zhang, Y.; Liu, X.; Li, G.; Tang, W. "Synthesis of Chiral α-Amino Tertiary Boronic Esters by Enantioselective Hydroboration of α-Arylenamides" *J. Am. Chem. Soc.,* **2015**, *137*, 6746.

(29) Shoba, V. M.; Thacker, N. C.; Bochat, A. J.; Takacs, J. M. "Synthesis of Chiral Tertiary Boronic Esters by Oxime-Directed Catalytic Asymmetric Hydroboration" *Angew. Chem., Int. Ed.,* **2016**, *55*, 1465.

(30) Bochat, A. J.; Shoba, V. M.; Takacs, J. M. "Ligand-Controlled Regiodivergent Enantioselective Rhodium-Catalyzed Alkene Hydroboration" *Angew. Chem., Int. Ed.,* **2019**, *58*, 9434.

(31) Leonori, D.; Aggarwal, V. K. "Reagent-Controlled Lithiation–Borylation" in *Synthesis and Application of Organoboron Compounds*, Topics in Organometallic Chemistry, **2015**, *49*, 271.

(32) Pulis, A. P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. "Synthesis of Enantioenriched Tertiary Boronic Esters by the Lithiation/Borylation of Secondary Alkyl Benzoates" *J. Am. Chem. Soc.,* **2013**, *135*, 16054.

(33) Pulis, A. P.; Aggarwal, V. K. "Synthesis of Enantioenriched Tertiary Boronic Esters from Secondary Allylic Carbamates. Application to the Synthesis of C30 Botryococcene" *J. Am. Chem. Soc.,* **2012**, *134*, 7570.

(34) Watson, C. G.; Aggarwal, V. K. "Asymmetric Synthesis of 1-Heteroaryl-1-arylalkyl Tertiary Alcohols and 1-Pyridyl-1-arylethanes by Lithiation–Borylation Methodology" *Org. Lett.,* **2013**, *15*, 1346.

(35) Partridge, B. M.; Chausset-Boissarie, L.; Burns, M.; Pulis, A. P.; Aggarwal, V. K. "Enantioselective Synthesis and Cross-coupling of Tertiary Propargylic Boronic Esters Using Lithiation-Borylation of Propargylic Carbamates" *Angew. Chem., Int. Ed.,* **2012**, *51*, 11795.

(36) Aggarwal, V. K.; Binanzer, M.; Ceglie, M. C. D.; Gallanti, M.; Glasspoole, B. W.; Kendrik, S. J. F.; Sonawane, R. P.; Vázquez-Romero, A.; Webster, M. P. "Asymmetric Synthesis of Tertiary and Quaternary Allyl- and Crotylsilanes via the Borylation of Lithiated Carbamates" *Org. Lett.,* **2011**, *13*, 1490.

(37) Dang, L.; Lin, Z.; Marder, T. B. " DFT Studies on the Borylation of α,β-Unsaturated Carbonyl Compounds Catalyzed by Phosphine Copper(I) Boryl Complexes and Observations on the Interconversions between O- and C-Bound Enolates of Cu, B, and Si" *Organometallics*, **2008**, *27*, 4443.

(38) Radomkit, S.; Hoveyda, A. H. "Enantioselective Synthesis of Boron-Substituted Quaternary Carbon Stereogenic Centers through NHC-Catalyzed Conjugate Additions of (Pinacolato)boron Units to Enones" *Angew. Chem., Int. Ed.,* **2014**, *53*, 3387.

(39) Brown, H. C.; Rao, B. C. S. "A new technique for the conversion of olefins into organoboranes and related alcohols" *J. Am. Chem. Soc.,* **1956**, *78*, 5694.

(40) The Nobel Prize in Chemistry 1979. NobelPrize.org. Nobel Media AB 2019. Fri. 31 May 2019.

(41) Wilczynski, R.; Sneddon, L. G. "Transition Metal Catalyzed Reactions of Alkynes and Boron Hydrides: Synthesis of 2-(cis-2-Butenyl)pentaborane(9) and its Conversion into Monocarbon Carboranes" *J. Am. Chem. Soc.,* **1980**, *8*, 2857.

(42) Männig, D.; Nöth, H. "Catalytic Hydroboration with Rhodium Complexes" *Angew. Chem., Int. Ed.,* **1985**, *24*, 878.

(43) (a) Hayashi, T.; Matsumoto, Y.; Ito, Y. "Catalytic asymmetric hydroboration of styrenes" *J. Am. Chem. Soc.,* **1989**, *111*, 3426; (b) Sato, M.; Miayura, N.; Suzuki, A. "Rhodium(i)-catalyzed asymmetric hydroboration of alkenes with 1,3,2-benzodioxaborole" *Tett. Lett.,* **1990**, *31*, 231.

(44) Crudden, C. M.; Edwards, D., "Catalytic Asymmetric Hydroboration: Recent Advances and Applications in Carbon–Carbon Bond-Forming Reactions" *Eur. J. Org. Chem.,* **2003**, *24*, 4695.

(45) Smith, S. M.; Thacker, N. C.; Takacs, J. M. "Efficient Amide-Directed Catalytic Asymmetric Hydroboration" *J. Am. Chem. Soc.,* **2008**, *130*, 3734.

(46) O'Brien, P. "Recent advances in asymmetric synthesis using chiral lithium amide bases" *J. Chem. Soc., Perkin Trans. 1,* **1998**, 1439.

(47) Bagutski, V.; Elford, T. G.; Aggarwal, V. K. "Synthesis of Highly Enantioenriched C-Tertiary Amines From Boronic Esters: Application to the Synthesis of Igmesine" *Angew. Chem., Int. Ed.,* **2011**, *50*, 1080.

(48) Edelstein, E. K.; Grote, A. C.; Palkowitz, M. D.; Morken, J. P. "A Protocol for Direct Stereospecific Amination of Primary, Secondary, and Tertiary Alkylboronic Esters" *Synlett*, **2018**, *29*, 1749.

(49) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. "Protodeboronation of Tertiary Boronic Esters: Asymmetric Synthesis of Tertiary Alkyl Stereogenic Centers" *J. Am. Chem. Soc.*, **2010**, *132*, 17096.

(50) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. "A convenient stereoselective synthesis of substituted alkenes via hydroboration-iodination of alkynes" *J. Am. Chem. Soc.*, **1967**, *89*, 3652.

(51) Armstrong, R. J.; García-Ruiz, C.; Myers, E. L.; Aggarwal, V. K. "Stereodivergent Olefination of Enantioenriched Boronic Esters." *Angew. Chem., Int. Ed.*, **2017**, *56*, 786.

(52) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. "Enantioselective Construction of Quaternary Stereogenic Centers from Tertiary Boronic Esters: Methodology and Applications" *Angew. Chem., Int. Ed.*, **2011**, *50*, 3760.

(53) Brown, H. C. and Srebnik, M. "Organoboranes. 50. Preparation and characterization of organyl-1-alkynylborinic esters" *Organometallics*, **1987**, *6*, 629.

(54) Wang, Y.; Noble, A.; Myers, E. L.; Aggarwal, V. K. "Enantiospecific Alkynylation of Alkylboronic Esters" *Angew. Chem., Int. Ed.*, **2016**, *55*, 4270.

(55) Blair, D. J.; Fletcher, C. J.; Wheelhouse, K. M. P.; Aggarwal, V. K. "Stereocontrolled Synthesis of Adjacent Acyclic Quaternary-Tertiary Motifs: Application to a Concise Total Synthesis of (−)-Filiformin" *Angew. Chem., Int. Ed.*, **2014**, *53*, 5552.

(56) Pulis, A. P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. "Synthesis of Enantioenriched Tertiary Boronic Esters by the Lithiation/Borylation of Secondary Alkyl Benzoates" *J. Am. Chem. Soc.,* **2013**, *135*, 16054.

(57) Watson, C. G.; Balanta, A.; Elford, T. G.; Essafi, S.; Harvey, J. N.; Aggarwal, V. K. "Construction of Multiple, Contiguous Quaternary Stereocenters in Acyclic Molecules by Lithiation-Borylation" *J. Am. Chem. Soc.,* **2014**, *136*, 17370.

(58) Ros, A.; Aggarwal, V. K. "Complete stereoretention in the rhodium-catalyzed 1,2-addition of chiral secondary and tertiary alkyl potassium trifluoroborate salts to aldehydes" *Angew. Chem., Int. Ed.,* **2009**, *48*, 6289.

(59) Llaveria, J.; Leonori, D.; Aggarwal, V. K. " Stereospecific Coupling of Boronic Esters with N-Heteroaromatic Compounds" *J. Am. Chem. Soc.,* **2015**, *137*, 10958.

(60) Ganesh, V.; Odachowski, M.; Aggarwal, V. K. "Alkynyl Moiety for Triggering 1,2-Metallate Shifts: Enantiospecific sp^2-sp^3 Coupling of Boronic Esters with p-Arylacetylenes" *Angew. Chem., Int. Ed.,* **2017**, *56*, 9752.

(61) Wilson, C. M.; Ganesh, V.; Noble, A.; Aggarwal, V. K. "Enantiospecific sp^2-sp^3 Coupling of ortho- and para-Phenols with Secondary and Tertiary Boronic Esters" *Angew. Chem., Int. Ed.,* **2017**, *56*, 16318.

(62) Ganesh, V.; Noble, A.; Aggarwal, V. K. "Chiral Aniline Synthesis via Stereospecific C(sp3)–C(sp2) Coupling of Boronic Esters with Aryl Hydrazines" *Org. Lett.,* **2018**, *20*, 6144.

(63) Horsman, G. P.; Zechel, D. L. "Phosphonate Biochemistry" *Chem. Rev.,* **2017**, *117*, 5704.

(64) Web: https://www.viread.com/

(65) C&EN cover story "Drug structures displayed for the first time in Orlando" April 5, 2019.

(66) Corey, E. J.; Kwiatkowski, G. T. "The Synthesis of Olefins from O,O'-Dialkyl β-Lithioalkylphosphonothioate Esters" *J. Am. Chem. Soc.,* **1966**, *88,* 5654.

(67) Tan, J.; Cheon, C. H.; Yamamoto, H. "Construction of Vicinal Tertiary and All Carbon Quaternary Centers by Catalytic Asymmetric Claisen Rearrangement of Enolphosphonates" *Angew. Chem., Int. Ed.,* **2012**, *51,* 8264.

(68) Chary, B. C.; Kim, S. "Rhodium(III)-catalyzed ortho-olefination of aryl phosphonates" *Org. Biomol. Chem.,* **2013**, *11,* 6879.

(69) Zhao, D.; Nimphius, C.; Lindale, M.; Glorius, F. "Phosphoryl-Related Directing Groups in Rhodium(III) Catalysis: A General Strategy to Diverse P-Containing Frameworks" *Org. Lett.,* **2013**, *15,* 4504.

(70) Bera, M.; Sahoo, S. K.; Maiti, D. "Room-Temperature meta-Functionalization: Pd(II)-Catalyzed Synthesis of 1,3,5-Trialkenyl Arene and meta-Hydroxylated Olefin" *ACS Catal.* **2016**, *6,* 3575.

(71) (a) Cui, P.; McCalmont, W. F.; Tomsig, J. L.; Lynch, K. R.; Macdonald, T. L. "α- and β-Substituted phosphonate analogs of LPA as autotaxin inhibitors" *Bioorg. Med. Chem.,* **2008**, *16,* 2212. (b) Cui, P.; Tomsig, J. L.; McCalmont, W. F.; Lee, S.; Becker, C. J.; Lynch, K. R.; Macdonald, T. L. "Synthesis and biological evaluation of phosphonate derivatives as autotaxin (ATX) inhibitors" *Biorg. Med. Chem. Lett.,* **2007**, *17,* 1634. (c) Ordonez, M.; Gonzalez-Morales, A.; Salazar-Fernandez, H. "Highly diastereoselective reduction of β-ketophosphonates bearing homochiral bis(α-methylbenzyl)amine: preparation of both enantiomers of phosphogabob (GABOBP)" *Tetrahedron: Asymmetry* **2004**, *15,* 2719.

CHAPTER TWO: PHOSPHONATE-DIRECTED CATALYTIC ASYMMETRIC HYDROBORATION OF DISUBSTITUTED VINYL ARENES

2.1. Metal-catalyzed CAHB of 1,1-disubstituted (methylidene) vinyl arenes: results with iridium, cobalt and copper catalysts

The substrate class of 1,1-disubstituted (methylidenes) alkenes has been widely explored in the field of CAHB. However, achieving high levels of enantioinduction in this substrate class has been historically challenging owing to the inability of a chiral reagent or catalyst to effectively discriminate between the enantiotopic faces of such barely prochiral substrates. Recent catalyst developments for efficient CAHB of 1,1-disubstituted vinyl arenes have focused on using iridium, cobalt or copper with pinacolborane (pinBH) or pinacol diborane (B_2pin_2). Boron delivery occur at the less substituted carbon atom of the alkene (Figure 2.1). For example, the Hoveyda group developed a NHC(**L1**)-Cu catalyzed enantioselective net protoboration of α-methyl styrene derivatives (Fig. 2.1 A).[1] This transformation is proposed to occur via an initial borocupration of the alkene which results in boron delivery to the less substituted terminus of the alkene and that of copper delivery to the more substituted benzylic site. The benzyl-copper intermediate eventually undergoes protonolysis to form the final product and the copper-catalyst re-enters the catalytic cycle. The Mazet group developed an iridium-catalyzed CAHB of similar substrates using pinacolborane (Fig. 2.1 B).[2] The active catalyst is formed in situ via the combination of the iridium-precatalyst $[Ir(OMe)(cod)]_2$ and the P,N-bidentate ligand **L2**. Terminal regioselectivity leading to β-chiral primary boronic esters were formed. Similar regioselectivity is also observed under conditions developed by Huang group (Fig. 2.1 C) wherein the cobalt complex **C1** bearing bulky chiral oxazoline pyridine mediates the

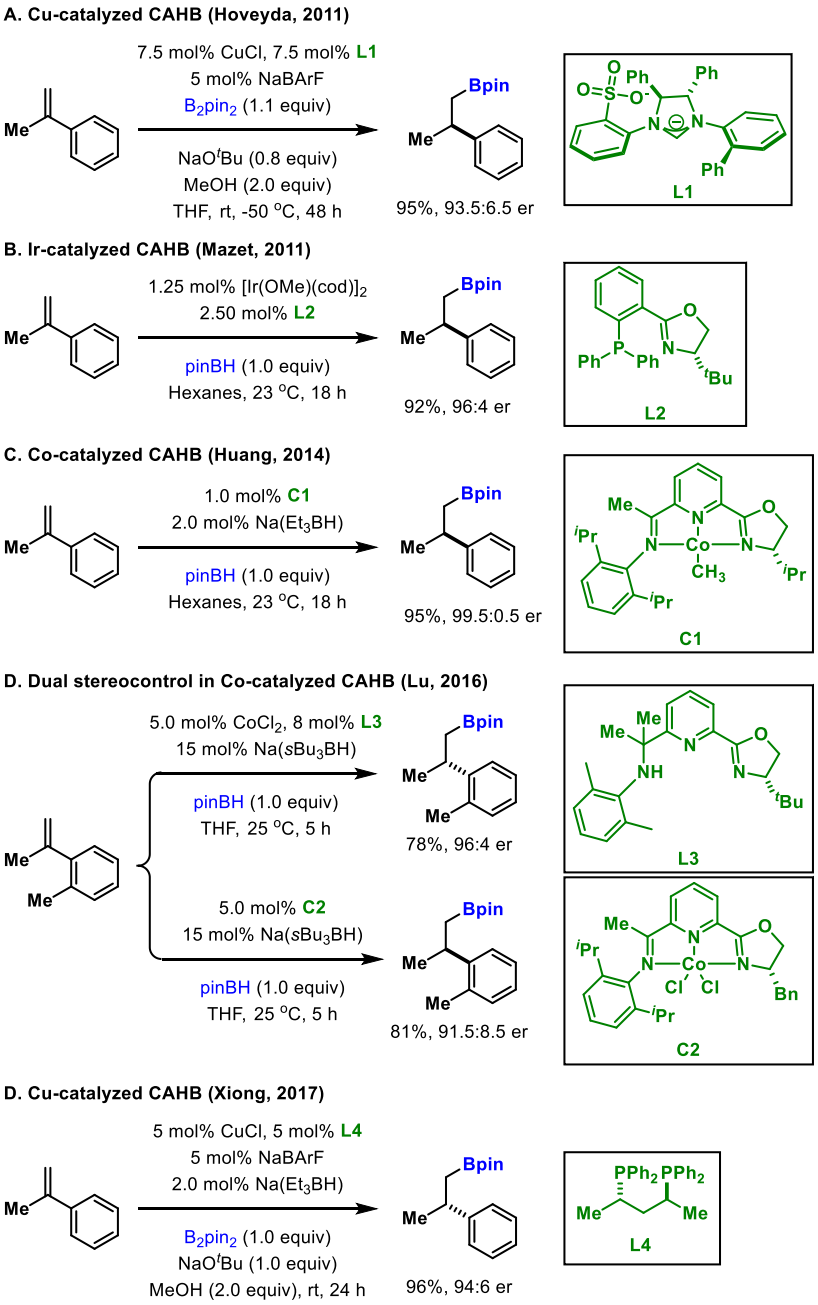


Figure 2.1. Selected examples of transition-metal catalyzed CAHB of methylidene vinyl arenes.

---

reaction.[3] In yet another case of cobalt catalyzed CAHB of α-methyl styrene derivatives, Lu disclosed the possibilities of forming enantiomers of the product by simply changing

the nature of the chiral oxazoline ligand moiety (Figure 2.1 D).[4] Depending on whether the active catalyst is formed via the more flexible amine group (**L3**) or the rigid imino group (**C2**), catalysis occurs under mechanistically distinct pathways affording the enantiomeric products. Yet another remarkable example of copper-catalyzed CAHB of 1,1-disubstituted vinyl/bisvinyl arenes was developed by the Xiong group (Figure 2.1 E).[5] The bidentate ligand **L4** with a smaller bite angle in conjugation with a copper precatalyst was used for efficient net protoboration in this case.

2.2. Development of Rh-catalyzed, directed-CAHB of methylidene vinyl arenes: comparison of amide, oxime and phosphonate-directing groups[6]

The Takacs group has been exploring the rhodium-catalyzed, directed CAHB of functionalized alkene substrates with the goal of obtaining multifunctional, chiral boronic ester synthons. Several factors influence the regio and stereochemical outcomes of these reactions. For instance, the nature of the directing group, the alkene substitution pattern, the alkene substituent and the chiral ligand all play pivotal roles. The directed-CAHB of functionalized alkenes is catalyzed by a chiral rhodium catalyst prepared in-situ from a combination of a commercially available rhodium precatalyst such as $Rh(nbd)_2BF_4$ and a TADDOL- or BINOL-derived chiral cyclic phosphite or phosphoramidite. Alternatively, the rhodium-precatalyst can be generated in-situ using a combination of $[Rh(cod)Cl]_2$ and $AgBF_4$ in a 1:2 ratio; this precatalyst can be effectively used as a substitute for the commercially available precatalyst $Rh(nbd)_2BF_4$. The latter method is more economical. Furthermore, we also find that the TADDOL- and BINOL-derived chiral ligands are highly

complementary in their effectiveness, their efficiency hinges, in part, on the substrate's alkene substitution pattern.

Using the TADDOL-derived phosphite (*R*,*R*)-**T1** in combination with a Rh-precatalyst, the amide and oxime-directed CAHB of β-aryl, β,γ-unsaturated vinyl arene substrates **1** and **3** results in boration at the less substituted terminus of the alkene, affording functionalized γ-borated products (*S*)-**2** (71%, 96.5:3.5 er) and (*R*)-**4** (70%, 95:5 er), respectively (Fig. 2.2).[7] The regiochemical outcomes for amide- and oxime-directed CAHB are similar to those obtained using iridium, cobalt or copper catalysts (Sec. 2.1), that is, boron addition occurs at the less substituted terminus of the alkene for methylidene substrates bearing at least one aryl substituent.

Incorporating a phosphonate-functionality in otherwise similar β-aryl (or heteroaryl) substituted methylidene substrates leads to boron delivery predominantly to the more substituted carbon of the alkene undergoing reaction.[6] For example, substrate **5a** undergoes efficient CAHB using the TADDOL-derived chiral cyclic phosphite (*R*,*R*)-**T1** to yield chiral tertiary benzylic boronic ester (*R*)-**6a** (80%, 95:5 er) as the major product. This result constitutes the first reported example of boron delivery to the more substituted carbon atom of an aryl substituted methylidene in the literature. Although the regioselectivity is opposite to that for the amide- and oxime-directed CAHB reactions, the sense of stereochemistry remains the same, that is, B-H adds to the *si*-face (top-face in the perspective shown in Figure 2.2) of the alkene.

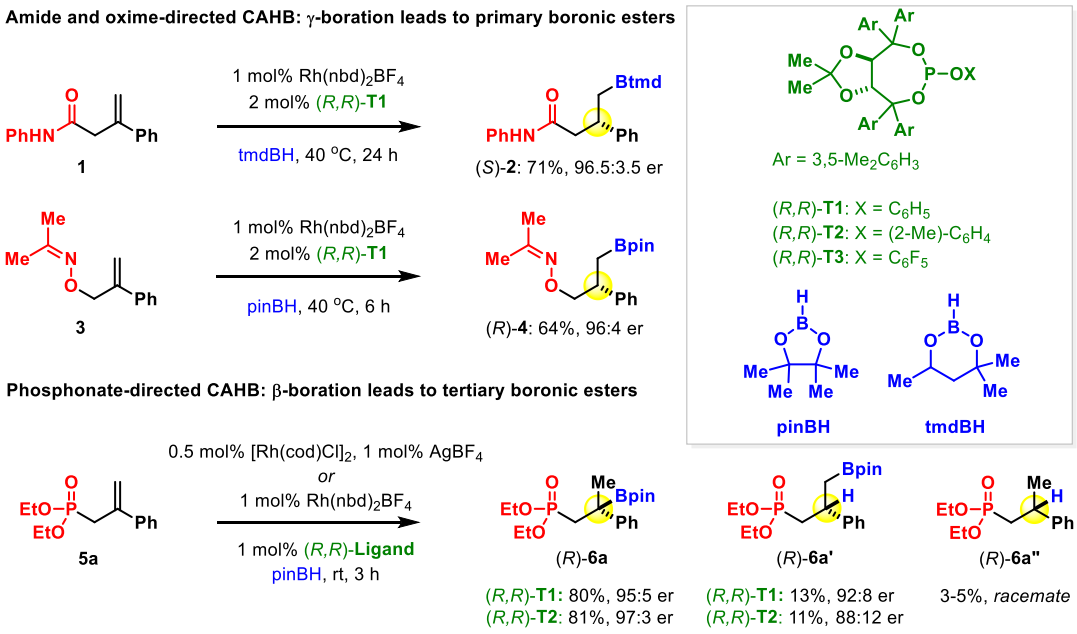


Figure 2.2. Directed CAHB of methylidene vinyl arenes: Comparison of amide, oxime and phosphonate-directing groups. (Adapted with permission from Ref. 6. Copyright 2018 American Chemical Society)

While **6a** is the major product obtained in the CAHB of phosphonate-functionalized substrate **5a**, the reaction leads to a distribution of products. The minor regioisomer **6a'** (13%, 92:8 er) and the alkene reduction product **6a"** (3-5%, racemate) are also formed under the reaction conditions. The minor regioisomer **6a'** is formed with the same sense of π-facial selectivity as that of the major regioisomer **6a**. This outcome contrasts results with what was observed from our previous studies where we found that a change in regioselectivity is usually coupled with a change in π-facial selectivity under the typical CAHB conditions.[8] The alkene reduction product **6a"** is formed in trace quantities under CAHB conditions and its formation is a subject of ongoing studies.[9] Its formation as a racemate implies its origin from a competing catalytic cycle and is believed to occur in the

presence of adventitious moisture. From our studies, we have found that the amount of alkene reduction product also varies between different substrate classes and is significantly dependent on the nature of borane as well (See Chapter 5: Ligand screening data). For instance, using tmdBH for the phosphonate-functionalized substrate **5a**, significant amounts (*ca.* >40%) of the reduction side product is obtained.

2.3. Experimental data probing into the origin of unusual regioselectivity observed[6]

The contrasting regiochemical results obtained with the phosphonate-functionalized methylidene vinyl arene substrate **5a** naturally raises the question as to whether the phosphonate-directing group is solely responsible for the observed β-boration regiochemistry leading to chiral tertiary boronic esters. This does not appear to be the case. We have carried out CAHB reactions on several analogs of **5a** to obtain information regarding the influence of the directing group, the nature of the alkene substituent and that of the distance between the directing group and the alkene in the overall regiochemistry observed. Substrates bearing *ortho*- substituted phenyl groups (*e.g.* **5b** and **5c**) lead to a complete reversal of regioselectivity (Figure 2.3).

In these cases, CAHB occurs with predominant γ-boration leading to chiral primary boronic esters **6b** (82%, 78:22 er) and **6c** (80%, 74:26 er) in exclusive regioselectivity but poor levels of enantioinduction under the reaction conditions. The alkene reduction product accounts for the majority of the mass balance in these two cases. While the regioselectivity changes, the sense of π-facial selectivity obtained from substrates **5b** and **5c** (*i.e.*, top-face) is similar to that obtained from the phenyl substituted

parent substrate **5a**. We speculate that ortho substitution results in regioselectivity reversal because of the increased steric hindrance for boration at the β-position.

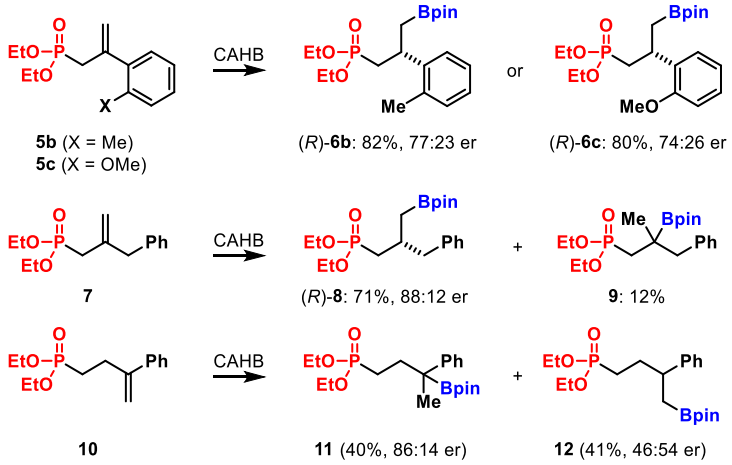


Figure 2.3. Variations in regioselectivity observed for some methylidene substrates. Standard CAHB conditions: 1 mol% $Rh(nbd)_2BF_4$, 1 mol% (*R*,*R*)-**T2**, pinBH, rt. 3-12 h. Note: Yields and er's were determined after oxidation to the corresponding alcohols. (Adapted with permission from Ref. 6. Copyright 2018 American Chemical Society)

Substrate **7** is similar to **5** except that the substituent at the β-position is an alkyl rather than an aryl group (*i.e.*, benzyl vs. phenyl). Under standard CAHB conditions, substrate **7** leads to the formation of the γ-borated product (*R*)-**8** (71%, 88:12 er) as the major product. Formation of the chiral primary boronic ester **8** occurs via predominant *si*-face (top-face in the perspective shown). The minor regioisomer **9** (12%) along with traces of the alkene reduction product accounts for majority of the mass balance in the CAHB of alkyl-substituted substrate **7**.

The CAHB results obtained from substrate **7** indicates the need for an aryl substituent at the β-position for the observed regiochemistry in **5a**. To probe into the role of proximity of the phosphonate-functionality in directing the course of the reaction, we

subjected substrate **10**, the one carbon homologue of **5a** to standard reaction conditions. Unlike the high levels of regioselectivity (5:1) obtained for substrate **5a**, the homologous substrate **10** affords a 1:1 mixture of the two possible regioisomers with neither regioisomer exhibiting high levels of enantioselectivity. Therefore, the results compiled in figure 2.4 indicate that the phosphonate group, as well as its disposition relative to the alkene and the nature of the alkene substituent (*i.e.*, the need for conjugation) combine to control the regio and enantioselectivity observed in phosphonate-directed CAHB of 1,1-disubstituted vinyl arenes.

It can be noted, that for most of the chiral borated phosphonates, the overall polarity of the molecule is due to the phosphonate functionality. Therefore, separation of regioisomeric boronic esters prove difficult in several cases. The isolation of the chiral boronic esters from the minor regioisomers or the alkene reduction products were difficult for examples shown in Figure 2.3. Oxidation of the purified hydroboration mixture results in a mixture of regioisomeric alcohols and the alkene reduction side product which are easily separable from each other. The yields and the corresponding enantiomer ratios for the compounds in Figure 2.3 were obtained after oxidation to the corresponding alcohols.

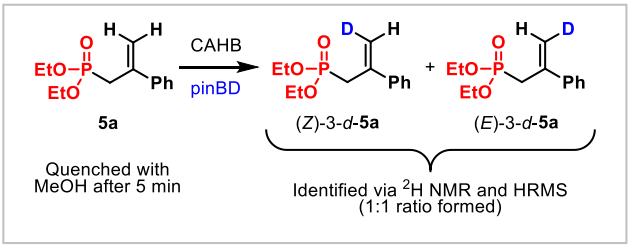
2.4. Mechanistic insights into phosphonate-directed CAHB of 1,1-disubstituted vinyl arenes

The results presented in section 2.3 revealed the crucial role of several structural components of the allyl phosphonate substrate **5a** that leads to the observed β-boration regiochemistry in CAHB. The identified factors that results in the observed regiochemistry forming chiral tertiary boronic esters are (1) the unique directing ability of the phosphonate

functionality, (2) the need for conjugation at the β-position of the methylidene substrate undergoing reaction, (3) lack of substitution at the ortho-position of the aromatic ring attached to the alkene, and (4) the appropriate positioning of the directing group with respect to the alkene for efficient chelation to the chiral rhodium catalyst. If any of these factors is not satisfied in the substrate, then boron is not delivered to the more substituted position of the alkene in the event of CAHB. We carried out deuterium labelling experiments using pinBD for CAHB of **5a** to systematically probe into the mechanism of the reaction.

Deuterium incorporation into substrate was found when a CAHB mixture of **5a** and pinBD was quenched before complete reaction (*ca.* after 5 minutes into the reaction) with methanol (Figure 2.4). ^{2}H-NMR and HRMS analyses of the crude CAHB mixture helped identify the monodeuterated species (*Z*)-3-*d*-**5a** and (*E*)-3-*d*-**5a** that were formed in roughly a 1:1 ratio. The dideuterated species 3,3-d_2-**5a** was not observed. We have considered two mechanistic scenarios for the incorporation of deuterium in substrate (Figure 2.4). Pathway 1 considers migratory insertion of the alkene to Rh-D forming a 3^{o}-benzyl rhodium intermediate **Im-1**. The latter subsequently undergoes β-H elimination to form (*Z*)-3-*d*-**5a** and (*E*)-3-*d*-**5a**. Pathway 2 is another mechanistic possibility suggested by our colleague Moraiah Locklear. Pathway 2 considers the possibility of a directed C-H insertion of the rhodium complex at the γ-position to form **Im-2**.[10] Subsequent C-D reductive elimination from **Im-2** should lead to the formation of (*Z*)-3-*d*-**5a**. This pathway, however, cannot explain the formation of (*E*)-3-*d*-**5a**. Since we get a 1:1 mixture of the isomeric deuterium incorporated products (*Z*)-3-*d*-**5a** and (*E*)-3-*d*-**5a**, the dominant pathway for incorporation of deuterium in the substrate is most likely pathway 1. Deuterium incorporation data

implies that (1) the alkene coordination and borane oxidative addition to the chiral rhodium catalyst are reversible, and (2) deuterium incorporation into the substrate followed by substrate decomplexation and the reductive elimination of borane from the rhodium catalyst generates pinBH. The in-situ generated pinBH in the event of deuterium incorporation into substrate further is confirmed by the identification of products formed from pinBH incorporation to substrate.



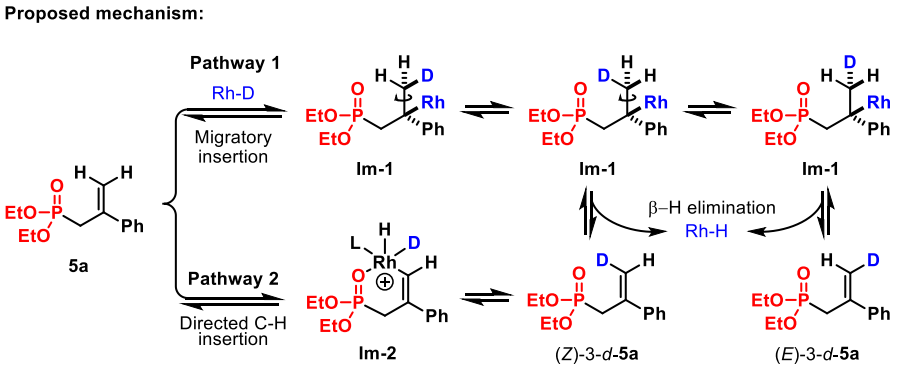


Figure 2.4: Deuterium incorporation seen in substrate under standard CAHB conditions.

Deuterium incorporation into substrate was further verified when the products obtained from the CAHB/oxidation of **5a** with pinBD (a 2:1 ratio of the regioisomeric alcohols **13a** and **13a'** was obtained) were analyzed using a combination of ^{1}H, ^{2}H, ^{13}C, ^{13}C-DEPT135 NMRs and HRMS techniques (Figure 2.5). Analysis of the chiral tertiary alcohol product **13a** (obtained via oxidation of the tertiary boronic ester **6a**) enabled identification of three different species with varying levels of deuterium incorporation: (1)

the non-deuterated product **13a** (18%), (2) the mono-deuterated product 3-*d*-**13a** (74%), and (3) the dideuterated product 3,3-d_2-**13a** (8%). The non-deuterated product **13a** is thought to form via CAHB of **5a** with pinBH followed by oxidation (the latter generated in-situ from reversible pinBD addition to the alkene followed by substrate decomplexation and reductive elimination of pinBH). The mono-deuterated product 3-*d*-**13a** is expected to form via CAHB of **5a** with pinBD followed by oxidation, or via CAHB of (*E*/*Z*)-3-*d*-**5a** with pinBH (generated in-situ) followed by oxidation. The dideuterated product 3,3-d_2- presumably arises from the CAHB of (*E*/*Z*)-3-*d*-**5a** with pinBD followed by oxidation.

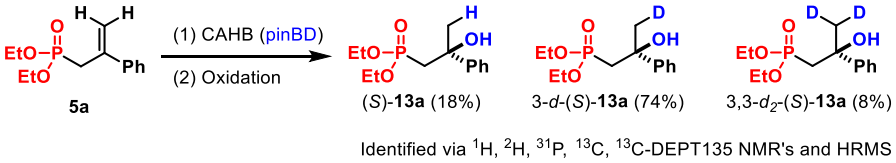


Figure 2.5: Different levels of deuterium incorporation observed in the major (tertiary) alcohol product obtained via CAHB of **5a** with pinBD followed by oxidation

---

Analysis of the minor regioisomeric primary alcohol product formed via CAHB/oxidation of **5a** with pinBD also shows varying levels of deuterium incorporation (Figure 2.6). A total of four species were identified: (1) the non-deuterated product **13a'** (21%), (2) the mono-deuterated product 2-*d*-**13a'** (60%), (3) the mono-deuterated product 3-*d*-**13a'** (9%), and (4) the dideuterated product 2,3-d_2-**13a'** (10%). The non-deuterated product **13a'** arises via CAHB of **5a** with pinBH (generated in-situ from H/D exchange of the substrate) followed by oxidation. The monodeuterated product 2-*d*-**13a'** is presumably formed via CAHB of **5a** with pinBD followed by oxidation. However, the monodeuterated product 3-*d*-**13a'** is formed via CAHB of (*E*/*Z*)-3-*d*-**5a** with pinBH (generated in-situ) followed by oxidation. The dideuterated product arises via CAHB of (*E*/*Z*)-3-*d*-**5a** with

pinBD followed by oxidation. The different levels of deuterium incorporation in the minor (primary) alcohol product formed via CAHB of **5a** with pinBD followed by oxidation further confirm the initial incorporation of deuterium in the starting material and thus support the reversibility of initial Rh-(H/D) addition to the substrate as well as reversibility of pinB(H/D) oxidative addition to the chiral rhodium catalyst.

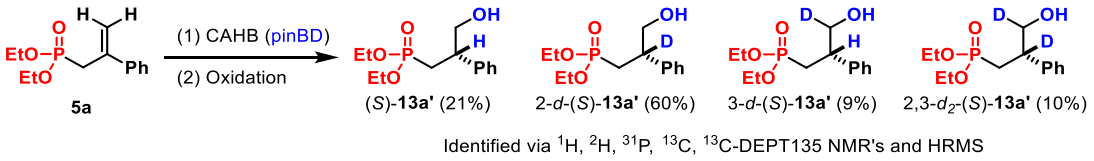


Figure 2.6: Different levels of deuterium incorporation observed in the minor (primary) alcohol product obtained via CAHB of **5a** with pinBD followed by oxidation

---

The results of double labelling experiments[11] carried out by our former colleague Dr. Sean M. Smith also support a mechanism of Rh-catalyzed CAHB consistent with oxidative addition of borane the metal center. Oxidative addition of B-H bonds to Rh-complexes have been experimentally supported and the complexes resulting from oxidative addition have been isolated and characterized.[12] Based on this data and the results obtained using deuterium labelling experiments, a mechanism explaining the formation of chiral tertiary boronic esters via phosphonate-directed CAHB of methylidene vinyl arene substrates such as **5a** is proposed in Figure 2.7. The proposed mechanism begins with the cationic TADDOL-ligated rhodium complex undergoing oxidative addition with pinBH to form Im-1. This step is expected to be reversible based on the data obtained from deuterium labelling experiments. Im-1 undergoes substrate coordination via a two-point binding (*i.e.*, chelation) with the phosphonate as well as the alkene undergoing reaction to form Im-2. Im-2 undergoes migratory insertion into the Rh-H bond to form Im-3 which features a 3^{o}-

alkyl rhodium intermediate (η^1 σ-benzyl complex). Im-3 is expected to be in equilibrium with its corresponding η^3 π-benzyl complex, the formation of which explains the regioselectivity observed with vinyl arenes.[20] Im-3 can undergo β-H elimination to go back to Im-2 or it can undergo reductive elimination of C-B bond to form the chiral tertiary boronic ester product and the catalyst re-enters the catalytic cycle. The reductive elimination step is expected to be rate-determining as other steps in the catalytic cycle are reversible.

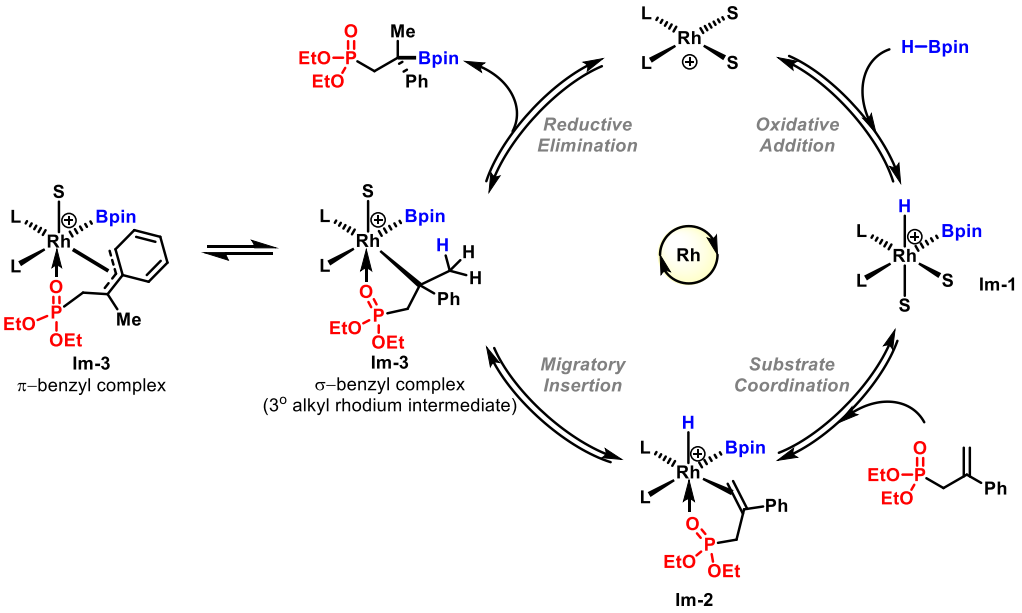


Figure 2.7: Proposed mechanism explaining formation of chiral tertiary boronic esters via phosphonate directed CAHB of methylidene vinyl arenes.

The mechanism proposed in Figure 2.7 is consistent with the deuterium labelling experiments and suggests that migratory insertion of the C=C bond to a Rh-H/D bond occurs first in the catalytic cycle. This can explain the insertion of deuterium into a substrate via initial addition to a Rh-D bond followed by β-H elimination to form a Rh-H intermediate. However, this mechanism requires invoking a sterically congested tertiary-

alkyl rhodium intermediate. An alternative mechanistic proposal was along the lines of alkene insertion into a Rh-B occurring first to construct the tertiary boronic ester, followed by reductive elimination to construct the C-H bond at the γ-position. However, deuterium labelling experiments suggested this is not in fact the case and insertion into Rh-H occurs first.

Yet another experimental evidence for the existence of tertiary-alkyl-rhodium intermediates in the catalytic cycle came from the results of competition CAHB experiments between substrates bearing donor and acceptor groups appended to the arene at the β-position with sub stoichiometric amount of borane (Figure 2.8). When a 1:1 mixture of substrates **5d** and **5e** bearing 4-methylphenyl and 4-trifluoromethylphenyl substituents at the β-position are subjected to standard CAHB conditions with 1 equivalents of pinBH, the substrate **5e** undergoes reaction twice as fast as compared to **5d**. This indicates that in case of **5e**, the tertiary alkyl rhodium intermediate is formed faster and undergoes rapid reductive elimination as compared to **5d**. This data provides an indirect evidence about the existence of a tertiary alkyl rhodium intermediate in the catalytic cycle. Figure 2.7A shows the ^{31}P NMR of a 1:1 mixture of **5d** and **5e** prior to undergoing CAHB. Figure 2.7B shows the ^{31}P NMR (zoomed in at the area where recovered substrates resonate) after standard CAHB of a 1:1 mixture of **5d** and **5e** with 1 equivalents of pinBH, showing a 2:1 ratio of **5d** and **5e**, showing faster consumption of **5e** as compared **5d**.

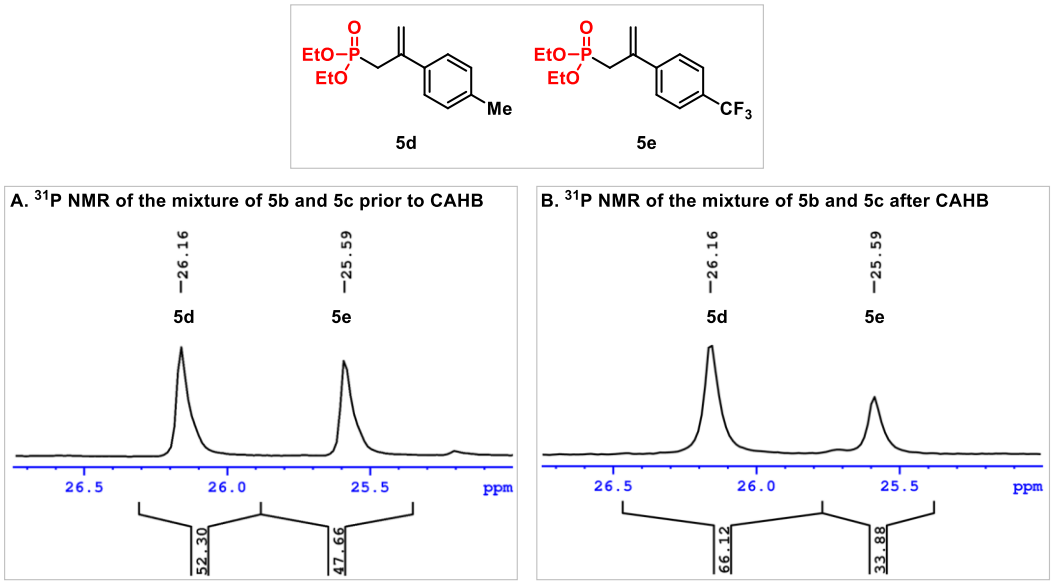


Figure 2.8: Competition CAHB reaction between methylidene substrates bearing donor (**5d**) vs. acceptor (**5e**) groups appended to the arene in the β-position of the substrate with sub-stoichiometric pinBH. **A.** ^{31}P NMR of the mixture of **5d** and **5e** prior to CAHB. **B.** ^{31}P NMR of the mixture of **5d** and **5e** after CAHB.

2.5. Substrate-scope of phosphonate-directed CAHB of methylidene vinyl arenes[6]

We subsequently turned our attention to the scope of substrates similar to **5a** varying in the electronic/steric characters of the aromatic ring appended to the alkene undergoing CAHB. Figure 2.9 summarizes the yields of chiral tertiary boronic esters obtained for a series of such substrates. For all documented cases, the major byproduct is the regioisomeric terminal boronic ester and traces of the alkene reduction product. The relative abundance of minor regioisomer and the reduced by-product are not easily determined by NMR in most of the cases. The enantiomer ratios are determined after oxidation to the corresponding chiral tertiary benzylic alcohols via chiral HPLC analysis.

The electronic character of the aryl group appended to the aromatic ring does not significantly affect the final outcome of CAHB. For instance, substrates bearing 4-methylphenyl (**5d**) and 4-trifluoromethylphenyl (**5e**) groups undergo CAHB with high efficiency, yielding chiral tertiary boronic esters **6d** (81%, 96:4 er) and **6e** (77%, 96:4 er), respectively. However, as demonstrated in Figure 2.8, the electronic nature of the aromatic ring does affect the relative turnover frequency. Substrates bearing 3-methoxyphenyl (**5f**) and 4-methoxyphenyl (**5g**) groups undergo efficient β-boration to yield the corresponding chiral tertiary benzylic boronic esters **6f** (76%, 97:3 er) and **6g** (70%, 94:6 er), respectively. Similarly, the catechol derivative **5h** and 3,5-dimethylphenyl bearing substrate **5i** undergo CAHB in good yield and with high levels of enantioinduction to afford the products **6h** (77%, 94:6 er) and **6i** (76%, 96:4 er), respectively.

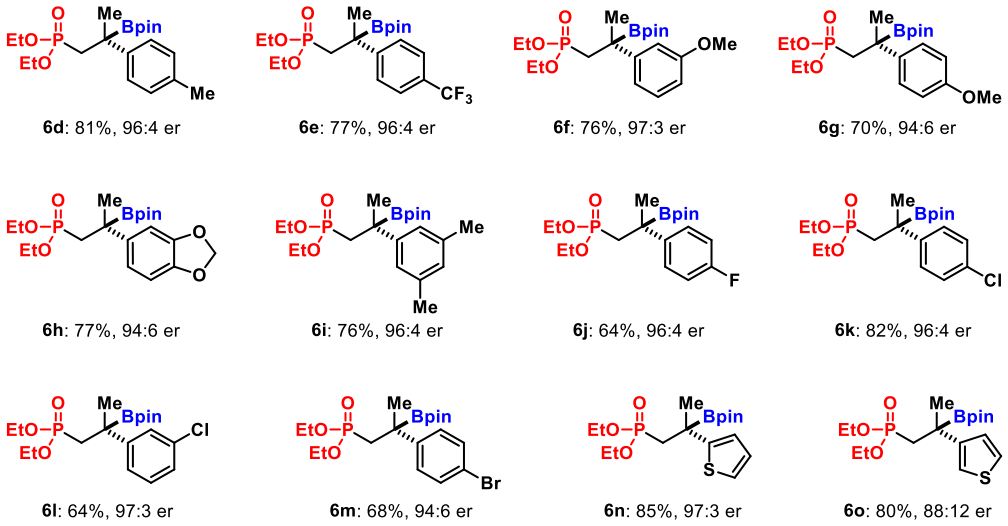


Figure 2.9. Substrate scope of phosphonate-directed CAHB of β-aryl methylidenes. Standard CAHB conditions: 1 mol% $Rh(nbd)_2BF_4$, 1 mol% (*R*,*R*)-**T2**, pinBH, rt. 3 h. Note: Yields and er's were determined after oxidation to the corresponding alcohols. (Adapted with permission from Ref. 6. Copyright 2018 American Chemical Society)

Aryl halides are versatile intermediates which can be subsequently refunctionalized via palladium-catalyzed cross-coupling protocols. We find that substrates bearing *meta*- or *para*- substituted phenyl substituents react smoothly under the standard conditions, albeit with some unusual variations in their regioselectivity. The corresponding β-borated products **6j-m** are obtained with high levels enantioselectivity (94:6 to 97:3 er) and in moderate to very good yields (62-82%). It is pleasing to note that the 4-bromophenyl derivative **5m** underwent CAHB without any apparent protodebromination, a competing transformation which is reported to occur under similar reaction conditions.[13]

Substrates derived from the heterocyclic thienyl ring system undergo highly regioselective β-boration in good yield. However, the enantioselectivity is dependent on the substitution at the thienyl moiety. For instance, the 2-thienyl derivative (**5n**) exhibits higher enantioselectivity than the corresponding 3-thienyl derivative (**5o**); the tertiary boronic ester products **6n** (85%, 97:3 er) and **6o** (80%, 88:12 er) are obtained, respectively. The reason behind the observed differences in the enantioselectivities obtained from the two thienyl substrates is unclear. One might reasonably expect the 3-thienyl derivative to perform better because the sulfur is positioned away from the site of unsaturation in the molecule as compared to the 2-thienyl derivative. However, similar observations were also noted in our work on CAHB of 1,2-disubstituted vinyl arenes (*vide infra*). The Hoveyda group also reported similar differences in the enantioselective addition of MEMO-substituted allyl-boron compounds catalyzed by organoboron-ammonium complexes to furan-derived aldimines differing in the substitution at the 2- or 3- position.[14]

2.6. Phosphonate-directed CAHB of 1,2-disubstituted vinyl arenes

As described above, the efforts of multiple groups have combined to achieve the development of effective catalysts for asymmetric protoboration or hydroboration of simple terminal and 1,1-disubstituted vinyl arenes (α-substituted styrene derivatives). However, the CAHB of the more functionalized 1,2-disubstituted vinyl arenes (β-substituted styrene derivatives) continues to be challenging as evidenced by a scarcity of literature reports. Therefore, there are few reports on the direct CAHB of 1,2-disubstituted vinyl arenes in the literature. In 2011, Prof. Yun's group reported an efficient copper-catalyzed CAHB of β-substituted styrene derivatives in which exclusive benzylic regioselectivity was observed (Figure 2.10).[15] The axially chiral ligand DTBM-SEGPHOS in conjugation with CuCl was used for efficient catalysis. In 2018, the Takacs group reported the amide-directed CAHB of δ-aryl-γ,δ-unsaturated substrates with pinacolborane, leading to direct access to chiral secondary benzylic δ-borated amide derivatives.[8] A simple BINOL-derived chiral cyclic phosphoramidite **B1** in conjugation with a commercially available rhodium precatalyst ($Rh(nbd)_2BF_4$) was used for efficient catalysis. The distal amide-functionality was shown to be crucial for achieving high levels of enantioselectivity.

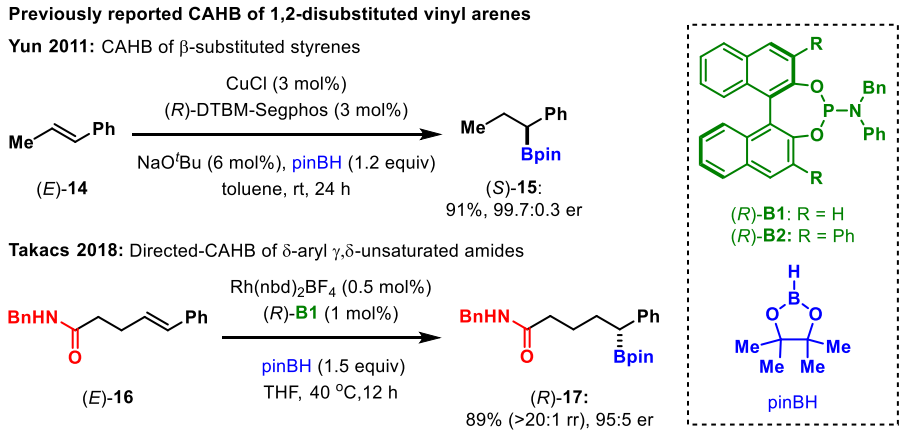


Figure 2.10. Previously reported examples of CAHB of 1,2-disubstituted vinyl arenes

In an effort to expand the substrate scope of phosphonate-directed CAHB of disubstituted alkenes, we envisioned the possibility of utilizing 1,2-disubstituted vinyl arenes bearing a directing group at the γ-position. Substrates of these types (*e.g.* **18a**) are structural isomers of the methylidene substrates bearing an aryl substitution at the β-position (*e.g.* **5a**). While the substrates of the latter type undergo rhodium-catalyzed CAHB with pinacolborane giving chiral tertiary boronic esters via regioselective β-boration, the isomeric γ-aryl substrates undergo highly regio and enantioselective γ-boration to afford new chiral, secondary benzylic boronic esters (Figure 2.11).[16] The choice of the chiral ligand is highly critical to the success of CAHB. Our studies consistently find that TADDOL-derived chiral phosphites and BINOL-derived chiral phosphoramidites tend to be complementary in their effectiveness; in part, the choice of the chiral ligand hinges on the substrate's alkene substitution pattern. While the rhodium catalyst systems incorporating TADDOL-derived phosphites were successful for efficient enantioinduction for β-aryl methylidene substrates such as **5a**, their use with the isomeric 1,2-disubstituted vinyl arenes such as **18a** gives the desired product in good yields (~80-82%) but with poor levels of enantioinduction (e.g. **T1**: 48:52 er, **T2:** 64:36 er). In contrast, the BINOL-derived phosphoramidites afford high levels of regiocontrol, yield and enantioselectivity with such substrates. For example, the ligand (*R*)- **B1** affords (*S*)-**19a** in good levels of enantiocontrol (90:10 er). From further ligand optimization, we identified the 3,3'-diphenyl derivative (*R*)-**B2** as the optimal ligand for this system. Its use with (*E*)-**18a** affords (*S*)-**19a** in excellent levels of enantiocontrol (96:4 er).

In the CAHB of 1,2-disubstituted vinyl arene (*E*)-**18a**, apart from the major regioisomeric secondary benzylic boronic ester **19a**, the minor regioisomer **19a'** (3-5%)

and the alkene reduction product **19a"** (10-15%) typically comprise the remaining mass balance. The regioisomeric ratio (rr) is the ratio of the major regioisomer (**19a**) and the minor regioisomer (**19a'**). Formation of the alkene reduction product is highly dependent on the nature of the substrate. For example, in case of the 1,1-disubstituted vinyl arene substrate **5a**, the alkene reduction product was formed in about 3-5% under the CAHB conditions. However, in case of the isomeric substrate (*E*)-**18a**, the alkene reduction product comprised 10-15% of the total reaction mass. The origin of the alkene reduction product under CAHB conditions is a subject of ongoing studies. Presence of adventitious moisture can lead to formation of the reduction side product.[9]

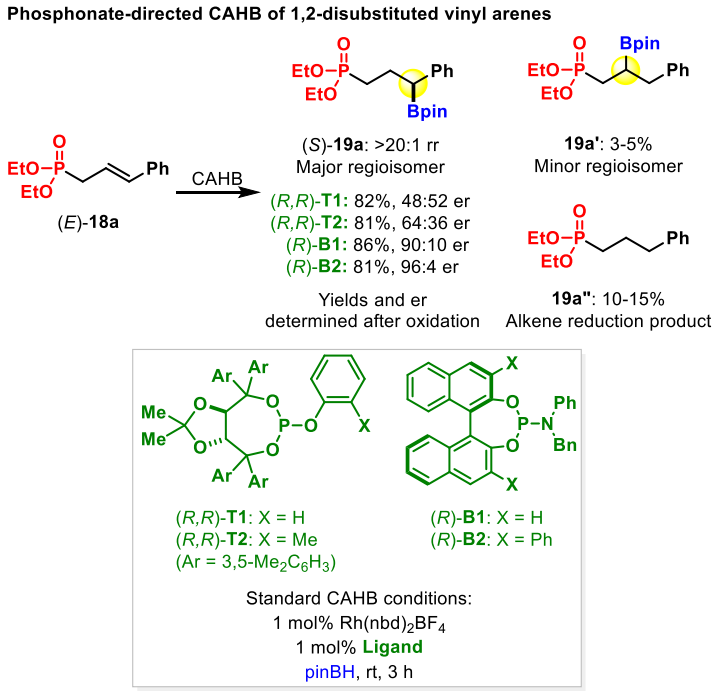


Figure 2.11. Phosphonate-directed CAHB of 1,2-disubstituted vinyl arenes. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

Our previous studies on amide-directed hydroboration of diastereomeric *E*- or *Z*-β,γ-unsaturated trisubstituted alkenes showed that B-H addition in CAHB is independent of alkene stereochemistry (Figure 2.12).[17] Diastereomeric products were obtained from stereoisomeric substrates. For example, CAHB of (*E*)-**20** with pinacolborane yields (3*R*,4*S*)-**21** and that of (*Z*)-**20** yields (3*R*,4*R*)-**21**.

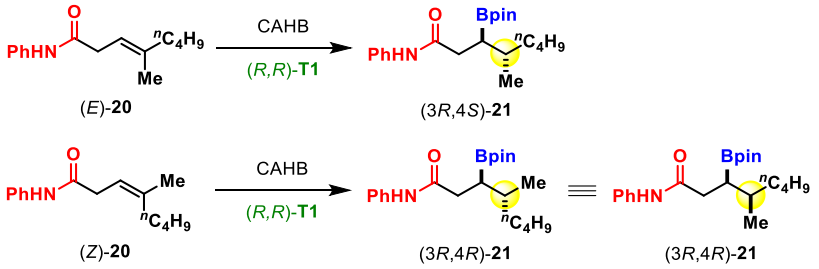


Figure 2.12. Amide-directed CAHB of (*E*)- or (*Z*)-trisubstituted alkenes affords diastereomeric products showing B-H addition is independent of alkene stereochemistry. (Adapted with permission from Ref. 17. Copyright 2010 American Chemical Society)

Based on the results obtained with the amide-directed CAHB of stereoisomeric (*E*)- and (*Z*)-trisubstituted alkene substrates **20**, we expected formation of enantiomeric products from phosphonate-functionalized 1,2-disubstituted vinyl arene substrates (*E*)- and (*Z*)-**18a** assuming B-H addition occurring to the same face irrespective of the alkene stereochemistry. However, we were surprised to find that the alkene stereochemistry did not impact the overall yield and stereochemistry in the CAHB of **18a**. The same major enantiomer of product (*S*)-**19a** is formed from either diastereomer of the substrate (Figure 2.13). Similar results were also obtained from the corresponding homologous vinyl arene substrates (*E*)- and (*Z*)-**23**.[15]

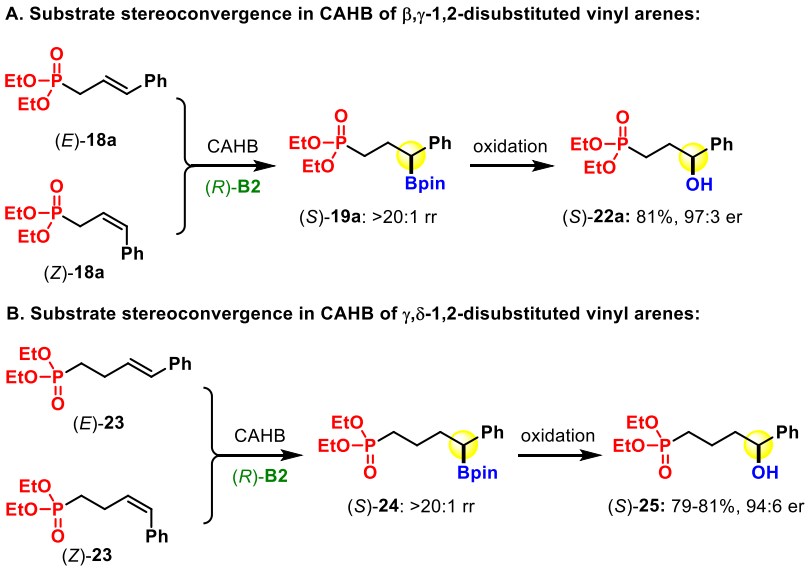


Figure 2.13. (*E*/*Z*)-Substrate stereoconvergence observed in the CAHB of phosphonate-functionalized 1,2-disubstituted vinyl arenes: same major enantiomer of product is formed from diastereomeric substrates. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

2.7. Experimental data explaining the origin of *E*/*Z*-stereoconvergence[16]

The discovery of (*E*/*Z*)-stereoconvergence in the CAHB of 1,2-disubstituted vinyl arenes adds an element of practical significance to the methodology since the product enantiopurity is independent of the substrate's alkene stereochemistry. The ability to arrive at the same major enantiomer of the product boronic ester starting with pure *E* or pure *Z* or any combination of an *E*/*Z*-mixture is highly practical but raises mechanistic questions. We speculated two possible scenarios that could explain the observed stereoconvergence: (1) *Z*- to *E*- substrate isomerization occurrs faster under the reaction conditions than the formation of B-H addition products. Hence essentially all product would arise from the *E* isomer only. (2) B-H addition occurs with opposite π-facial selectivity for the *Z* substrate

as compared to the *E* variant. The second possibility would be counterintuitive to the results obtained from trisubstituted amide substrates shown in Figure 2.12.

The origin of (*E*/*Z*)-isomer stereoconvergence is easily resolved based on the results of CAHB using a sub-stoichiometric quantity of pinBH (Figure 2.14) and results of deuterium labelling experiments, that is, CAHB of (*E*)- and (*Z*)-**18a** with pinBD (Figure 2.15). With respect to the first test, a sample enriched in (*Z*)-isomer of **18a** (9:1 *Z*:*E*) is subjected to the otherwise standard CAHB conditions, but using a limiting amount of pinBH (0.4 equiv.); the reaction, under such conditions leads to partial boration and recovered alkene. The ^{1}H spectral windows for the starting and recovered *E*/*Z* mixtures of **18a** shown in Figure 2.13 indicate that (*Z*)-**18a** is essentially completely converted to the (*E*)-isomer under the reaction conditions, thus suggesting a mechanistic pathway by which the two isomers lead to the same product.[18]

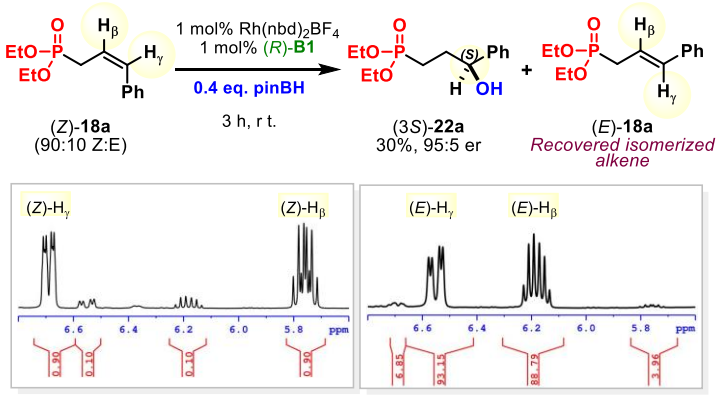


Figure 2.14. *Z*- to *E*- substrate isomerization is seen under standard CAHB conditions. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

Figure 2.15 shows the results of deuterium labelling which support the results obtained using a limiting amount of pinBH. Independently carried out CAHBs of (*E*)- and

(*Z*)-**18a** using pinBD results in different distributions of non-, isomeric mono- and di-deuterated products for the isomeric alkenes. CAHB/oxidation of (*E*)-**18a** using pinBD essentially forms a single monodeuterated product, tentatively assigned as 2-*d*-(2*S*,3*S*)-**22a** (83%) accompanied by the all proteo product (3*S*)-**22a** (17%); we find no evidence for dideuteration by mass spectral analysis. In contrast, CAHB/oxidation of (*Z*)-**18a** using pinBD yields about 30% of the non-deuterated product (3*S*)-**22a**, 47% of a mixture of diastereomeric monodeuterated products 2-*d*-(2*S*,3*S*)-**22a** and 2-*d*-(2*R*,3*R*)-**22a** and 21% of the dideuterated product 2,2-d_2-(3*S*)-**22a**. The dideuterated product presumably arises by the reaction of 2-*d*-(*E*)-**18a** with pinBD.

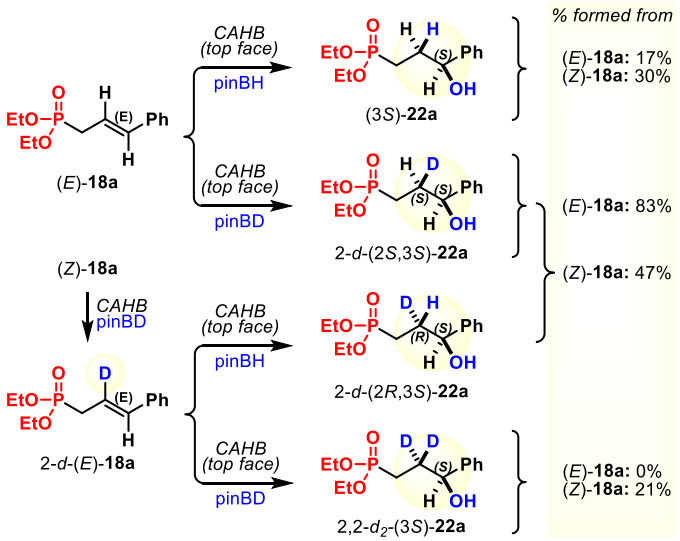


Figure 2.15. Different distributions of deuterated products are obtained when isomeric (*E*)- or (*Z*)-**18a** react with PinBD under standard CAHB conditions. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

2.8. Mechanistic insights in the CAHB of 1,2-disubstituted alkenes obtained from deuterium labeling experiments[16]

Rhodium-catalyzed pinBH addition to (*E*)-**18a** occurs from the *"top-face"* in the perspective drawn to form (3*S*)-**22a** (Figure 2.16; For absolute configuration assignments, see chapter 5). To systematically probe the origin of their stereoconvergent CAHB, we separately carried out deuterium labelling experiments via CAHB using pinBD followed by oxidation to analyze deuterated alcohol products for each stereoisomer of the substrate **18a** (Sec. 2.7). In this section, the mechanistic implications indicated by the results of deuterium labeling experiments is analyzed. In analogy to reaction with pinBH, CAHB of (*E*)-**18a** with pinBD proceeding via addition to the *"top face"* is assumed to give the 2-*d*-(2*S*,3*S*)-**22a** diastereomer. The site and extent of deuterium incorporated in **18a** were analyzed via ^{1}H, ^{2}H, ^{13}C, ^{13}C-DEPT 135 NMR and HRMS techniques.

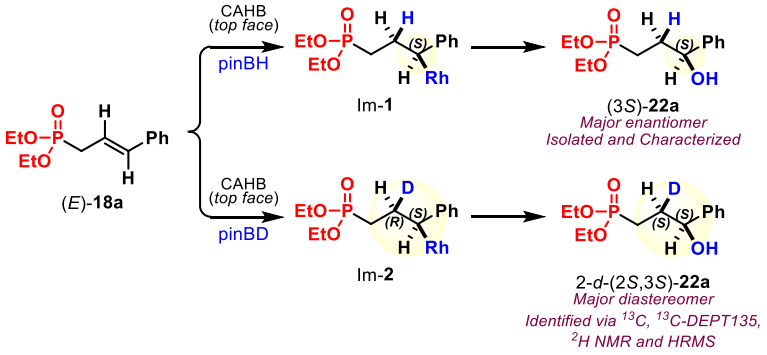


Figure 2.16. *"Top-face"* addition of pinBH and pinBD in the CAHB of (*E*)-**18a**. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

The ^{31}P NMR spectrum of (3*S*)-**22a** shows a single peak at 32.83 ppm (Spectrum A, Figure 2.16). However, the ^{31}P NMR spectrum of **22a** obtained from (*E*)-**18a** after CAHB with pinBD followed by oxidation shows two peaks at 32.85 ppm and 32.83 ppm in about 83:17 ratio (Spectrum B, Figure 2.17). The 32.85 ppm peak is assigned to 2-*d*-(2*S*,3*S*)-**22a** and that of 32.83 ppm for (3*S*)-**22a**. The formation of (3*S*)-**22a** must arise from

pinBH addition to (*E*)-**18a**; although completely deuterated pinBD is used, we speculate that some pinBH is formed under the reaction conditions. The mechanism of pinBH formation under the conditions described is unclear.

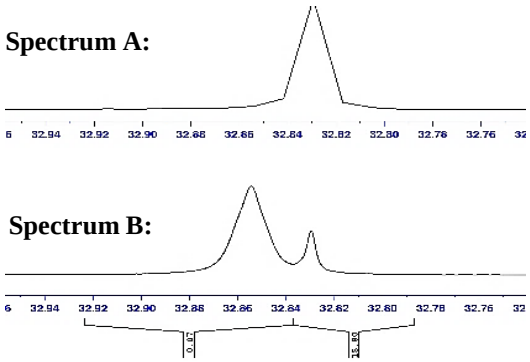


Figure 2.17. ^{31}P NMR of (3*S*)-**22a** (Spectrum A) and enriched 2-d-(2*S*,3*S*)-**22a** (Spectrum B). (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

The peak for the β-carbon of (3*S*)-**22a** appears as a doublet at δ 32.02 ($^{2}J_{C\text{-}P}$ = 5.0 Hz; Spectra A, Figure 2.18) in the ^{13}C NMR spectrum. The ^{13}C NMR spectrum of **22a** obtained from (*E*)-**18a** after CAHB with pinBD followed by oxidation shows two peaks as shown in Spectra B (Figure 2.18). The β-carbon atom assigned to 2-*d*-(2*S*,3*S*)-**22a** bonded to deuterium and being two bonds away from phosphorus is identified at δ 31.66 in the ^{13}C NMR spectrum with a characteristic splitting pattern of a triplet of doublets ($^{1}J_{C\text{-}D}$ coupling ~ 20 Hz, $^{2}J_{C\text{-}P}$ coupling ~ 4.25 Hz): 31.66 (td, $^{1}J_{C\text{-}D}$ = 20 Hz, $^{2}J_{C\text{-}P}$ = 4.25 Hz) ppm. The peak at d 32.02 (d, $^{2}J_{C\text{-}P}$ = 5.0 Hz) is assigned to the non-deuterated product (3*S*)-**22a**. The ratio of deuterium to hydrogen in the β-carbon of **22a** obtained via CAHB of (*E*)-**18a** followed by oxidation is about 80:20 based on the ^{13}C and ^{31}P NMR spectra obtained.

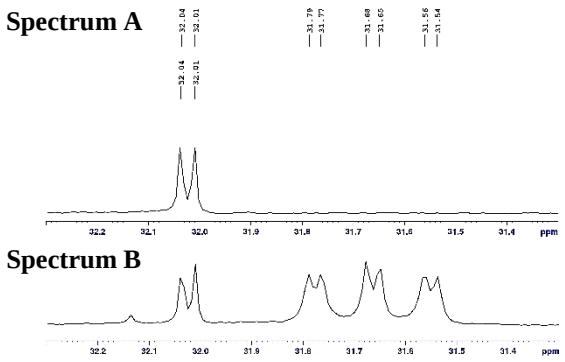


Figure 2.18. ^{13}C NMR spectra (zoomed in for β-carbon) of (3*S*)-**22a** (Spectrum A) and enriched 2-*d*-(2S,3S)-**22a** (Spectrum B). (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

In Figure 2.19, we consider the mechanistic consequences of *"top face"* and *"bottom face"* addition of pinBD to the isomeric (*Z*)-**18a** in light of the fact that it must ultimately produce deuterated (*S*)-**22a**, not deuterated (*R*)-**22a**. Addition of pinBD to the *"top-face"* of (*Z*)-**18a** would give rise to Im-**3**. Alternatively, addition of pinBD to the *"bottom face"* of (*Z*)-**18a** would give rise to Im-**4**. If subsequent steps in the mechanism leading to C–B bond formation were fast, Im-**3** would lead to deuterated (*R*)-**22a**, while Im-**4** would lead to the observed product, deuterated (*S*)-**22a**. However, as discussed in sec. 2.7, the (*E*/*Z*)-alkene isomerization occurring under the CAHB conditions can explain this (*E*/*Z*)-alkene geometry induced change in the sense of π-facial discrimination.

The formation of either Im-**3** or Im-**4** followed by rapid β-hydride elimination would lead to the formation of 2-*d*-(*E*)-**18a** which has been identified via ^{1}H and ^{2}H NMR analysis (Figure 2.20) from a reaction of (*Z*)-**18a** with pinBD that is quenched early with methanol. We find that isomerization of (*Z*)-**18a** is very rapid in the beginning of the

reaction; a nearly 1:1 ratio of *E:Z* substrates is identified in the first 5 minutes of the reaction time and then increases more slowly reaching a 2:1 ratio after about 30 minutes.

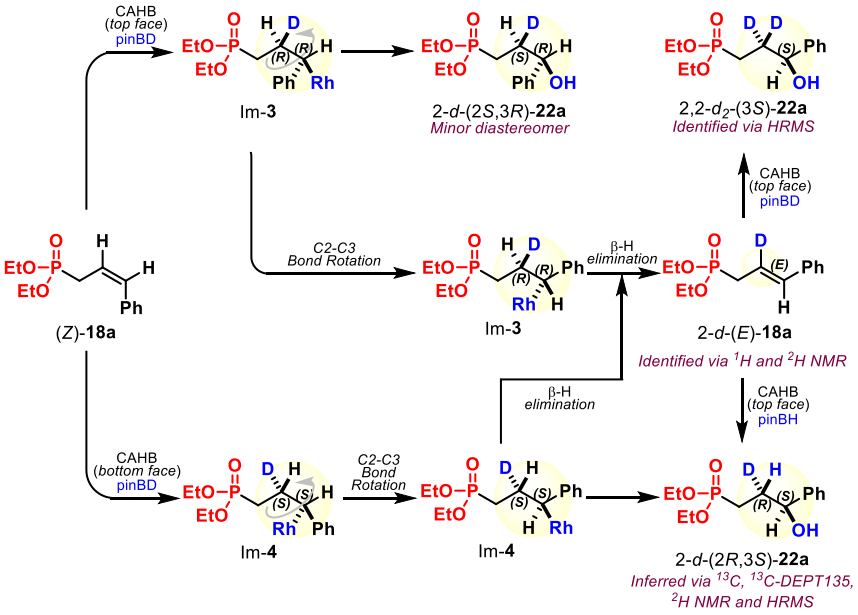


Figure 2.19. Top and bottom-face addition of pinBD in CAHB of (*Z*)-**18a** (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

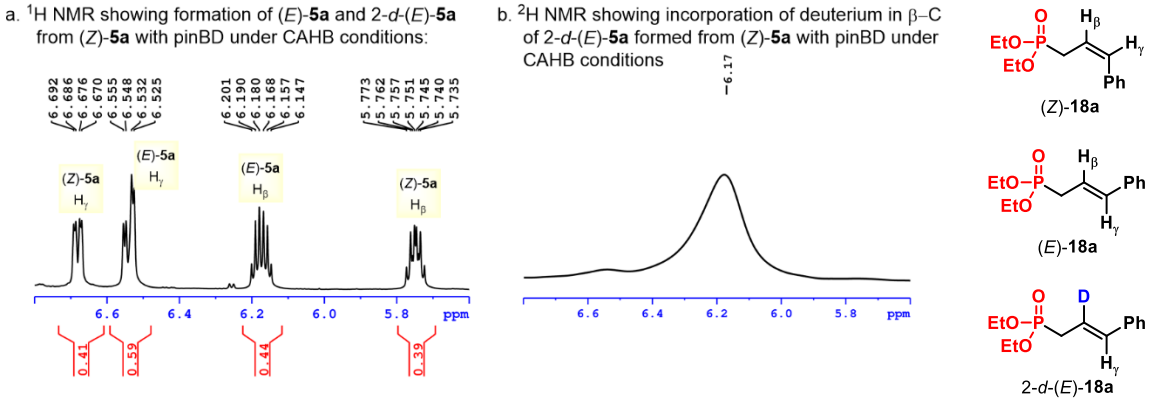


Figure 2.20. ^{1}H and ^{2}H NMR's showing formation of (*E*)-**18a** and 2-*d*-(*E*)-**18a** from (*Z*)-**18a** with pinBD under standard CAHB conditions. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

As shown in Figure 2.19, CAHB of 2-*d*-(*E*)-**18a** with pinBD from the expected *"top-face"* should result in the formation of 2,2-d_2-(3*S*)-**22a**, and the latter has been identified via HRMS analysis (vide infra). However, β-hydride elimination from Im-**3** or Im-**4** not only forms 2-*d*-(*E*)-**18a** but generates an equivalent amount of pinBH from pinBD. Therefore, we also find products resulting from this in situ generated pinBH; its expected addition to the *"top-face"* of 2-*d*-(*E*)-**18a** should afford 2-*d*-(2*R*,3*S*)-**22a** as illustrated in Figure 2.19. In addition, isomerization of (*Z*)-**18a** to (*E*)-**18a** via the with the initial addition of pinBH and then followed by pinBD addition, after oxidation, should generate the diastereomeric alcohol 2-*d*-(2*S*,3*S*)-**22a**. Finally, the addition of pinBH to in situ generated (*E*)-**18a** should generate a small amount of (3*S*)-**22a**. Thus, CAHB of (*Z*)-**18a** with pinBD should potentially lead to the formation of four possible products: (3*S*)-**22a**, 2-*d*-(2*R*,3*S*)-**22a**, 2-*d*-(2*S*,3*S*)-**22a** and 2,2-d_2-(3*S*)-**22a**. The ^{13}C NMR data shown in Figure 2.21 highlight the characteristic signatures for: **a**. (3*S*)-**22a**; **b.** 2-*d*-(2*S*,3*S*)-**22a** (as formed from (*E*)-**18a** with pinBD); and **c**. the mixture of 2-*d*-(2*S*,3*S*)-**22a** and 2-*d*-(2*R*,3*S*)-**22a** formed from (*Z*)-**18a** with pinBD in which the presence of 2-*d*-(2*R*,3*S*)-**22a** is inferred from the overlapping sets of ddd signals for the β-carbon bearing one deuterium from each of the two diastereomers.

The mixture of proteo/mono-deutero alcohols **22a** obtained via CAHB of (*E*)-**18a** with pinBD followed oxidation is subjected to HRMS (Figure 2.22). (i) The molecular ion peak for (3*S*)-**18a** (Calculated for $C_{13}H_{21}O_4P+Na^+$ = 295.1075) corresponds to a *m/z* peak at 295.1079 and that of 2-*d*-(2*S*,3*S*)-**18a** (Calculated for $C_{13}H_{20}DO_4P+Na^+$ = 296.1138) corresponds to a *m/z* peak at 296.1140. (ii) Since **18a** contains 13 C-atoms and the relative abundance of ^{13}C is 1.1% in nature, 14.3% of the area under the peak corresponding to *m/z*

295.1079 is subtracted from the area under the peak corresponding to *m/z* of 296.1140 to account for the ^{13}C correction. This gives a corrected area of 557640 under the peak corresponding to *m/z* of 296.1140 (molecular ion peak for 2-*d*-(2*S*,3*S*)-**22a**). The ^{13}C correction for area under the peak corresponding to *m/z* of 297.1180 would give a corrected area of 14808. This peak is mainly due to ^{13}C and not due to ^{2}H (See the elemental analysis). (iii) The ratio of (3*S*)-**22a** to 2-*d*-(2*S*,3*S*)-**22a** as obtained from the above HRMS analysis (Sample obtained from CAHB/Oxidation of (*E*)-**18a** with pinBD) is 17:83.

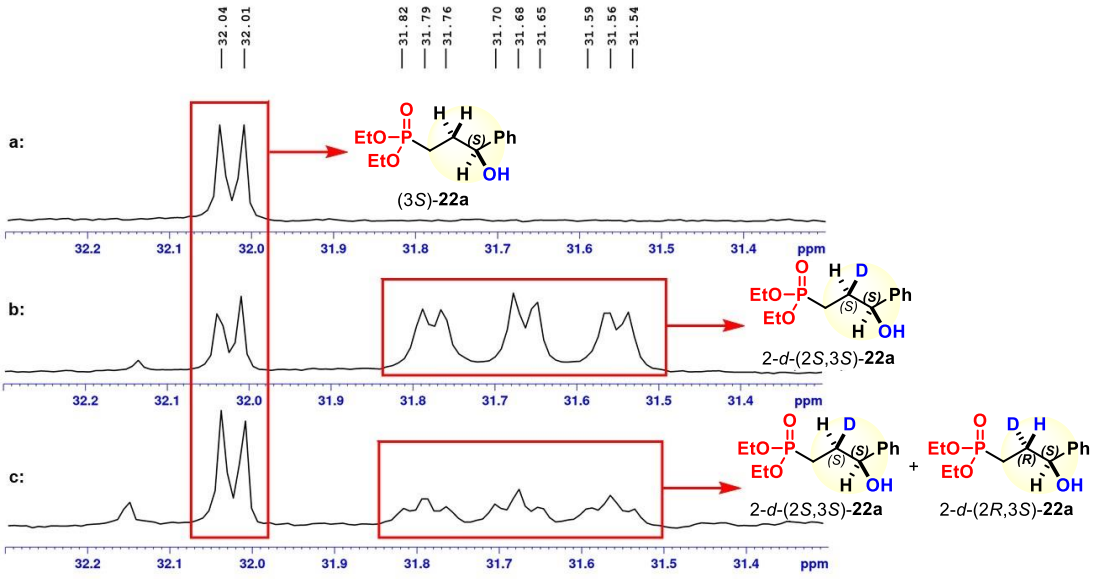
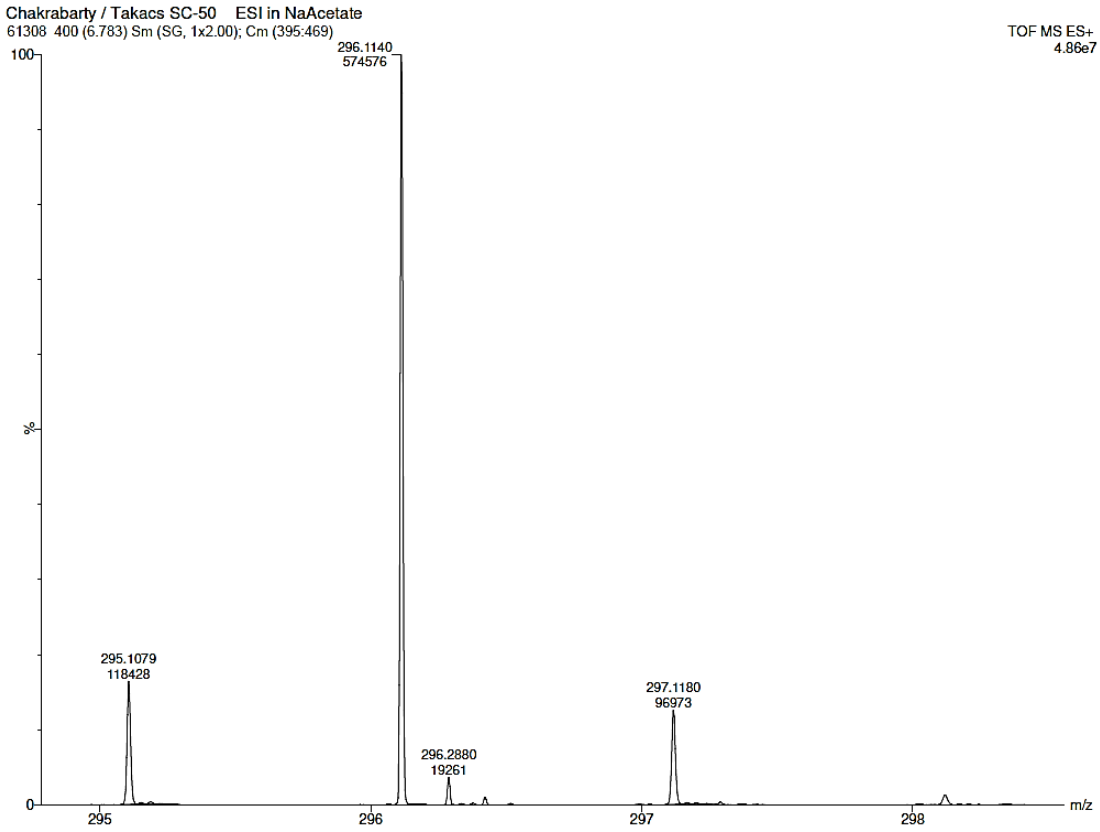
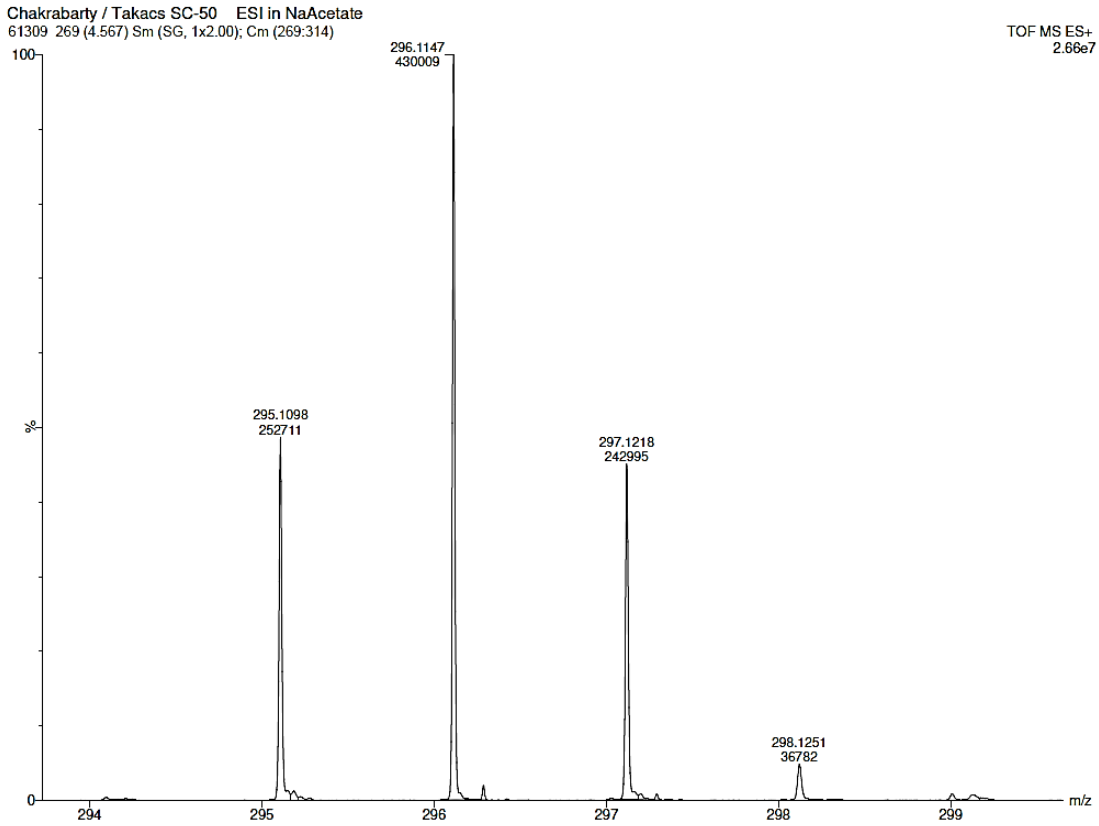


Figure 2.21. ^{13}C NMR zoomed in for the region of β-carbon: (a) CAHB of (*E*)-**18a** with pinBH, then oxidation to yield (3*S*)-**22a**. (b) CAHB of (*E*)-**18a** with pinBD, then oxidation to yield mixtures of hydro- and deutero incorporated **22a**. (c) CAHB of (*Z*)-**18a** with pinBD, then oxidation to yield diastereomeric monodeuterated **22a** in addition to hydro-incorporated **22a**. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)



Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
295.1075	16.28	295.1075	0.0	0.0	3.5	-1.$	n/a	1.#R	12C13 1H21 16O4 23Na 31P
		295.1097	-2.2	-7.5	4.5	-1.$	n/a	1.#R	12C12 13C 1H17 16O6 23Na 2H
		295.1099	-2.4	-8.1	12.5	-1.$	n/a	1.#R	12C20 1H16 16O 23Na
		295.1039	3.6	12.2	13.5	-1.$	n/a	1.#R	12C19 13C 1H13 16O 23Na 2H
296.1139	100.00	296.1138	0.1	0.3	3.5	-1.$	n/a	1.#R	12C13 1H20 16O4 23Na 2H 31P
		296.1132	0.7	2.4	12.5	-1.$	n/a	1.#R	12C19 13C 1H16 16O 23Na
		296.1162	-2.3	-7.8	12.5	-1.$	n/a	1.#R	12C20 1H15 16O 23Na 2H
		296.1109	3.0	10.1	3.5	-1.$	n/a	1.#R	12C12 13C 1H21 16O4 23Na 31P
		296.1191	-5.2	-17.6	3.5	-1.$	n/a	1.#R	12C12 13C 1H20 16O6 23Na
297.1177	12.63	297.1171	0.6	2.0	3.5	-1.$	n/a	1.#R	12C12 13C 1H20 16O4 23Na 2H 31P
		297.1195	-1.8	-6.1	12.5	-1.$	n/a	1.#R	12C19 13C 1H15 16O 23Na 2H
		297.1232	-5.5	-18.5	2.5	-1.$	n/a	1.#R	12C13 1H23 16O4 23Na 31P

Figure 2.22. HRMS analysis of the mixture of proteo/mono-deutero alcohols **22a** obtained via CAHB of (*E*)-**18a** with pinBD. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)



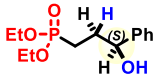
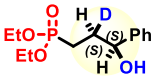
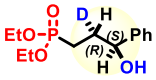
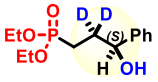
Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
295.1077	48.90	295.1075	0.2	0.7	3.5	-1.$	n/a	1.#R	12C13 1H21 16O4 23Na 31P
		295.1068	0.9	3.0	13.5	-1.$	n/a	1.#R	12C20 1H12 2H2 16O 23Na
		295.1097	-2.0	-6.8	4.5	-1.$	n/a	1.#R	12C12 13C 1H17 2H 16O6 23Na
		295.1099	-2.2	-7.5	12.5	-1.$	n/a	1.#R	12C20 1H16 16O 23Na
		295.1044	3.3	11.2	4.5	-1.$	n/a	1.#R	12C13 1H17 2H2 16O4 23Na 31P
		295.1039	3.8	12.9	13.5	-1.$	n/a	1.#R	12C19 13C 1H13 2H 16O 23Na
		295.1127	-5.0	-16.9	4.5	-1.$	n/a	1.#R	12C13 1H16 2H2 16O6 23Na
296.1138	100.00	296.1138	0.0	0.0	3.5	-1.$	n/a	1.#R	12C13 1H20 2H 16O4 23Na 31P
		296.1132	0.6	2.0	12.5	-1.$	n/a	1.#R	12C19 13C 1H16 16O 23Na
		296.1160	-2.2	-7.4	4.5	-1.$	n/a	1.#R	12C12 13C 1H16 2H2 16O6 23Na
		296.1162	-2.4	-8.1	12.5	-1.$	n/a	1.#R	12C20 1H15 2H 16O 23Na
		296.1109	2.9	9.8	3.5	-1.$	n/a	1.#R	12C12 13C 1H21 16O4 23Na 31P
		296.1101	3.7	12.5	13.5	-1.$	n/a	1.#R	12C19 13C 1H12 2H2 16O 23Na
		296.1191	-5.3	-17.9	3.5	-1.$	n/a	1.#R	12C12 13C 1H20 16O6 23Na
297.1197	44.90	297.1195	0.2	0.7	12.5	-1.$	n/a	1.#R	12C19 13C 1H15 2H 16O 23Na
		297.1201	-0.4	-1.3	3.5	-1.$	n/a	1.#R	12C13 1H19 2H2 16O4 23Na 31P
		297.1171	2.6	8.8	3.5	-1.$	n/a	1.#R	12C12 13C 1H20 2H 16O4 23Na 31P
		297.1224	-2.7	-9.1	12.5	-1.$	n/a	1.#R	12C20 1H14 2H2 16O 23Na
		297.1232	-3.5	-11.8	2.5	-1.$	n/a	1.#R	12C13 1H23 16O4 23Na 31P
		297.1254	-5.7	-19.2	3.5	-1.$	n/a	1.#R	12C12 13C 1H19 2H 16O6 23Na
		297.1255	-5.8	-19.5	11.5	-1.$	n/a	1.#R	12C20 1H18 16O 23Na

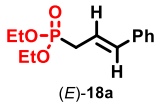
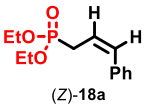
Figure 2.23. HRMS analysis of mixture of proteo/mono deutero and dideutero alcohols **22a** obtained via CAHB of (*Z*)-**18a** with pinBD. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

The mixture of proteo/mono deutero and dideutero alcohols **22a** obtained via CAHB of (*Z*)-**18a** with pinBD following CAHB/oxidation is subjected to HRMS (Figure 2.23). (i) The molecular ion peak for (3*S*)-**22a** (Calculated for $C_{13}H_{21}O_4P+Na^+$ = 295.1075) corresponds to a *m/z* peak at 295.1098, that of 2-*d*-(2*S*,3*S*)-**22a** (Calculated for $C_{13}H_{20}DO_4P+Na^+$ = 296.1138) corresponds to a *m/z* peak at 296.1147 and that of 2,2-d_2-(3*S*)-**22a** (Calculated for $C_{13}H_{19}D_2O_4P+Na^+$ = 297.1201) corresponds to a *m/z* peak at 297.1218. (ii) Since **22a** contains 13 C atoms and the relative abundance of ^{13}C is 1.1% in nature, 14.3% of the area under the peak corresponding to *m/z* 295.1098 is subtracted from the area under the peak corresponding to *m/z* of 296.1147 to account for the ^{13}C correction. This gives a corrected area of 393871 under the peak corresponding to *m/z* of 296.1147 (molecular ion peak for 2-*d*-(2*S*,3*S*)-**22a**). 14.3% of the corrected area under the peak corresponding to *m/z* 296.1147 is to be subtracted from the peak corresponding to *m/z* of 297.1218 to account for ^{13}C correction. Thus, the corrected area under *m/z* 297.1218 is 186671. (iii) Thus, the ratio of (3*S*)-**22a**: 2-*d*-(2*S*,3*S*)-**22a**: 2,2-d_2-(3*S*)-**22a** determined from HRMS analysis (Sample obtained from CAHB/Oxidation of (*Z*)-**18a** with pinBD) is 30: 47: 23.

Summary of deuterium-labeling experiments.

Following is the distribution of products that is obtained from (*E*)-**18a** and (*Z*)-**18a** when reacted with pinBD under standard CAHB conditions:

Substrate	Percentages inferred from NMR and HRMS analysis			
	 (3*S*)-**22a**	 2-*d*-(2*S*,3*S*)-**22a**	 2-*d*-(2*R*,3*S*)-**22a**	 2,2-d_2-(3*S*)-**22a**

 (*E*)-**18a**	17	83	--	--
 (*Z*)-**18a**	30	47		21

In conclusion, the same major enantiomer of chiral secondary benzyl alcohol **22a** is obtained from both (*E*)- and (*Z*)-**18a**. This (*E/Z*)-stereoconvergence during CAHB can be simply explained by the rapid isomerization of (*Z*)-**18a** to (*E*)-**18a** via initial addition of borane followed by β-hydride elimination under reaction conditions; this isomerization has been verified by deuterium labelling studies. However, it should be noted that the question of whether the (*E/Z*)-alkene geometry induces a change in the sense π-facial discrimination is not answered definitively by our experimental data. We can only conclude it is not necessary to invoke such a change to account for the observed experimental results.

2.9. Substrate-scope of phosphonate-directed CAHB of 1,2-disubstituted vinyl arenes[16]

Figure 2.24 summarizes results obtained for a series of 1,2-disubstituted vinyl arene substrates differing in the nature of the aromatic ring appended at the γ-position. In addition to the γ-borated product **19** and the minor regioisomeric β-borated product **19'**, alkene reduction (*i.e.*, **19"**) typically comprises the remaining 5-15% of the product mixture. The three products formed in the CAHB have distinct peaks in the ^{31}P NMR spectrum and the regioisomeric ratio (rr) of γ:β borated products is determined via ^{31}P NMR analysis of the crude CAHB mixture. The isolation of the major regioisomeric boronic ester (**19**) from the

minor regioisomeric boronic ester (**19'**) and the alkene reduction product (**19"**) is typically difficult as these have very similar R_f values. However, the isolation of the major regioisomeric alcohol (**22**) after oxidation of the mixture of CAHB products is quite feasible. Therefore, yields and enantiomer ratios are determined after oxidation. Alkene reduction under standard CAHB conditions arises from a competing catalytic cycle and is the subject of ongoing studies;[9] it will not be discussed further here. Herein, we focus on the regio- and enantioselectivity of the rhodium-catalyzed hydroboration mode.

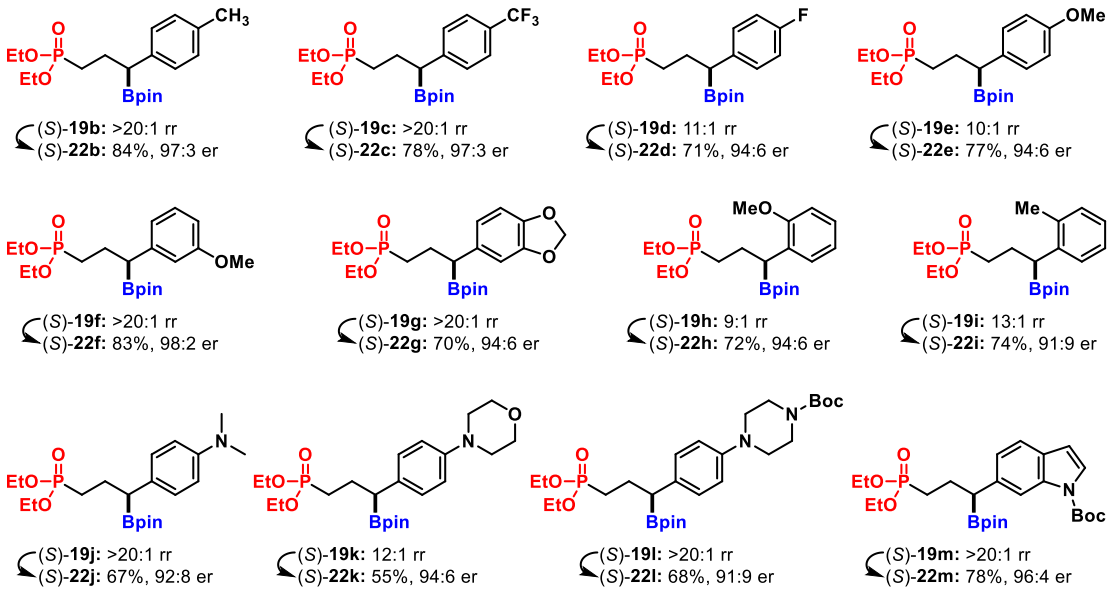


Figure 2.24. Scope of allyl phosphonate substrates bearing substituted benzene derivatives at the γ-position. Note: Yields and er determined after oxidation to the corresponding alcohols. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

A range of donor and acceptor substituents appended to the γ-phenyl group are well tolerated with minor fluctuations in regio and/or enantioselectivity. For example, the 4-methylphenyl derivative **18b** and the 4-trifluoromethylphenyl derivative **18c** undergo γ-

boration with high regioselectivity (>20:1 rr) yielding **22b** (84%, 97:3 er) and **22c** (78%, 97:3 er) after oxidation of the corresponding secondary benzylic boronic esters (*i.e.,* **19b** and **19c**). The 4-fluorophenyl (**18d**) and 4-methyoxyphenyl (**18e**) derivatives exhibit comparatively lower levels of γ:β regioselectivity (**19d**–**e**, 10-11:1 rr) and enantioselectivity affording **22d** (71%, 94:6 er) and **22e** (77%, 94:6 er), respectively. In contrast, the 3-methoxyphenyl derived substrate **18f** and 3,4-methylenedioxyphenyl derivative **18g** again exhibit higher regioselectivity (**19f-g:** >20:1 rr) and a range of enantioselectivity leading to **22f** (83%, 98:2 er) and **22g** (70%, 94:6 er), after oxidation.

Substrates bearing ortho-substituted phenyl groups (e.g. **18h-i**) undergo good conversion albeit with comparatively reduced regioselectivity (**19h**: 9:1 rr, **19i**: 13:1 rr) leading to **22h** (72%, 94:6 er) and **22i** (74%, 91:9 er). It is worth noting that unlike the results obtained with 1,1-disubstituted alkenes in which presence of an ortho substituent on the β-aryl group (e.g. **5n-o**) lead to a change in regioselectivity, substrates bearing 2-substituted arenes in this series of 1,2-disubstituted internal vinylarenes (e.g. **18h-i**) do not significantly impact the regioselectivity.

Substrates bearing basic nitrogen functionality appended to the aromatic ring at the γ-position undergo efficient reaction. For example, the substrates bearing 4-dimethylamino, morpholine, and pyrazine substituents **18i**–**k** demonstrate the viability of substrates bearing basic nitrogen functionality; **22i**–**k** are obtained in moderate to good yields (55-68%) and up to 94:6 er. The indole derivative **18l** exhibits high γ-regioselectivity (**19l**: >20:1 rr) in the event of CAHB and forms **22l** (78%, 96:4 er) in good yield and enantioselectivity.

In addition to demonstrating tolerance for basic nitrogen in several of the substrates described in Figure 2.24, it is important to note that CAHB is successful for substrates incorporating some common heterocyclic ring systems of high relevance in medicinal and pharmaceutical chemistry, albeit with some unusual variations in regio- and/or enantioselectivity (Figure 2.25). For example, the 3-substituted *N*-Boc-protected pyrrole derived substrate **18n** is both highly regioselective (**19n**: >20:1 rr) and highly enantioselective; the er obtained for **22n** (86%, 99:1 er) is the highest obtained among the set of substrates tested. However, the results obtained for CAHB of the 2-substituted *N*-Boc protected pyrrole derivative **18o** differ significantly. The regioselectivity of boronic ester **19o** (>20:1 rr) is excellent. However, the level of enantioselectivity for **22o** (85%, 80:20 er) is not only much lower but results from hydroboration with the opposite sense of π-facial selectivity compared to most other substrates (*vide infra*); (*R*)-**22o** is the major product. Other five-membered ring heteroaryl substituents also lead to surprising results. Compared to the results obtained for 3- and 2- substituted pyrrole derivatives, the 3- and 2-substituted thiophene substrates (*i.e.*, **18p** and **18q**) exhibit high regioselectivity leading to **19p** and **19q** (>20:1 rr), respectively. However, the 3-substituted thiophene **18p** affords **22p** (83%, 85:15 er) with only modest levels of stereocontrol while the 2-substituted thiophene derivative **18q** gives **22q** (80%, 95:5 er) with good stereocontrol. The enantioselectivity disparity from isomeric thiophene substrates is seen in case of the conjugated methylidene systems as well (e.g. **5l** vs. **5m**). The 2-substituted benzothiophene **18r** gives both lower levels of regiocontrol (**19r**, 5:1 rr) and enantioselectivity for **22r** (65%, 89:11 er).

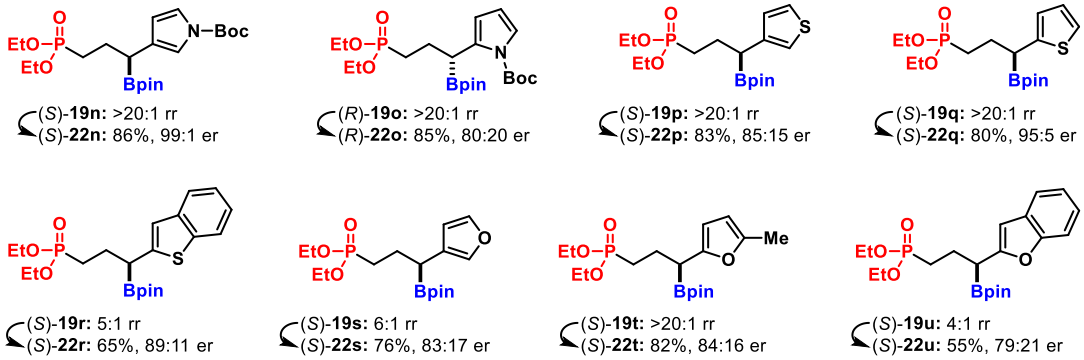


Figure 2.25. Scope of allyl phosphonate substrates bearing heterocyclic aromatic derivatives at the γ-position. Note: Yields and er determined after oxidation to the corresponding alcohols. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

The series of furan derivatives **18s**–**u** undergo CAHB with moderate levels of enantioinduction. Unlike the 2-substituted thiophene derivative **18q**, the corresponding 2-substituted furan derivative **18t** exhibits poor levels of enantioinduction. A similar observation was made in the asymmetric hydroboration of 2-vinyl furan by Brown and co-workers where the enantioselectivity of the product was surprisingly low as compared to the vinyl arenes derived from 6-membered aromatic rings.[19] Brown and co-workers proposed that the lower steric influence exerted by the smaller 2-furyl group resulted in the inability of the chiral catalyst to efficiently discriminate between the prochiral faces of the alkene leading to lower enantioselectivity. However, our results on the CAHB of benzofuran substrate **18u** leading to **19u** (55%, 79:21), again with moderate levels of enantioinduction shows that the steric effect may not be the primary cause for lower enantioselectivity. The lower levels of enantioselectivity could potentially stem from the

lower stability of the η^3 π-benzyl rhodium intermediates formed with these significantly electron rich furan derived substrates.[20]

One might reasonably question as to whether the phosphonate directing group is unique in promoting the γ-boration with these vinyl arene substrates. This, in fact, appears not to be the case. The corresponding benzylamide substrate (*E*)-**18v** undergoes regioselective γ-boration with (*R*)-**B1** to afford the analogous amide-functionalized, γ-borated benzylic boronic ester (*S*)-**19v** (7:1 rr) (Figure 2.25). Oxidation yields the chiral benzyl alcohol (*S*)-**22v** (78%, 94:6 er). In case of this amide substrate, we were surprised to find a unique ligand-dependent regioselection. The 3,3'-bisphenyl substituents in ligand **B1** play a significant role in determining regioselectivity. **B2**, the analogous BINOL-derived phosphoramidite derived from the parent BINOL ring system, gives a slight preference for β-boration (*ca.* 2:1 rr) with (*E*)-**18v**. However, with **B2**, the corresponding γ,δ-unsaturated amides such as (*E*)-**16** afford δ-borated benzylic boronic esters ((*R*)-**17**) in excellent yields and enantioselectivities.

The attempted CAHB of several other related phosphonates reveal some current limitations of the [$Rh(nbd)_2BF_4$/**B1**] catalyst system (Figure 2.26). In contrast to the vinylarene substrate (*E*)-**18a**, similar internal alkenes bearing an alkyl rather aryl/heteroaryl γ-substituent (e.g. (*E*)-**18w**), undergo predominantly β-boration, albeit with modest regio- and enantioselectivity with the standard catalyst system. The chiral secondary alkyl boronic ester (*S*)-**19w** (3:1 rr) is oxidized to yield the alcohol (*S*)-**22w** (60%, 75:25 er). The isomeric δ,ε-unsaturated vinyl arene (*E*)-**18x** affords the corresponding benzylic boronic ester (*S*)-**19x** upon CAHB, but again, with only modest regioselectivity (3:1 rr), yield, and enantiopurity (obtained after oxidation to (*S*)-**22x**: 47%, 88:12 er). The vinyl (*i.e.*, α,β-

unsaturated) phosphonate (*E*)-**18y** is largely recovered unreacted when subjected to the standard CAHB conditions. The trisubstituted variants (*E*)-**18z** and (*E*)-**18aa** only react sluggishly under the standard conditions. The benzylic regioisomer is preferred for these trisubstituted substrates. It should be noted that these results may reflect only the limitations of the [Rh(nbd)$_2$BF$_4$/(*R*)-**B2**] catalyst system; systematic catalyst optimizations have not been carried out for these substrates.

Substrate (*E*)-**18w**, however, reacts with pinBH using the catalyst formed from [Rh(nbd)$_2$BF$_4$/(*R*,*R*)-**T3**] with a similar regioselectivity as that obtained using [Rh(nbd)$_2$BF$_4$/(*R*)-**B2**], but with an improved enantioselectivity to form **22w** (60%, 94:6 er) after oxidation. The substrate (*E*)-**18aa** was also found to undergo reaction with [Rh(nbd)$_2$BF$_4$/(*R*,*R*)-**T2**] to form the corresponding benzylic regioisomer in a moderate enantioselectivity (65:35 er).

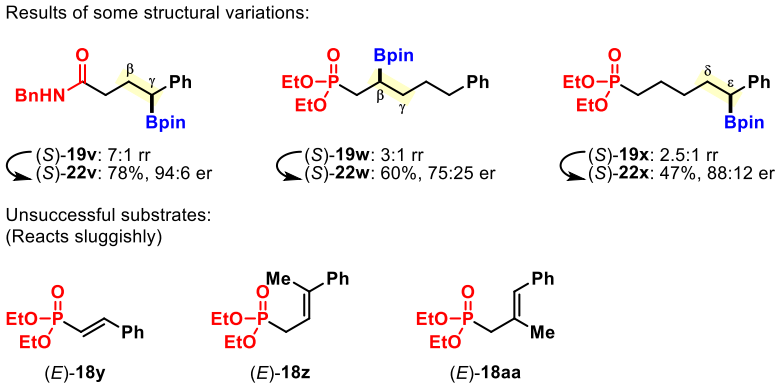


Figure 2.26. Additional substrate scope and some limitations of the methodology using the (*R*)-**B2**/Rh-catalyst system. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

2.10. Stereochemical assignments via kinetic resolution[16]

The variable regio- and stereochemical results obtained with several substrates bearing heteroaromatic ring systems in the CAHB of γ-aryl 1,2-disubstituted vinyl arenes illustrate a potential caveat for substrates bearing multiple donor groups in proximity of the alkene or those bearing relatively bulky extended aromatic ring systems. We used Birman's chiral cyclic thiourea (benzotetramisole (BTM))[21] acylation catalyst to employ a kinetic resolution (KR) strategy for confirming the absolute configuration assignments for several of the previously unreported chiral secondary benzylic alcohols **22** prepared via CAHB. As presented in Figure 2.27, the (*S*)-BTM catalyzed acylation of a racemic sample of **22a** with 0.5 equivalents of isobutyric anhydride results in the rapid acylation of (*S*)-**22a** to (*S*)-**26a** and recovery of the known (*R*)-**22a** unreacted alcohol.[22]

Alcohol **22** and the corresponding isopropyl-ester **26** are readily differentiated by ^{31}P NMR spectroscopy providing a convenient protocol for the rapid determination of absolute configuration of some of these previously unreported chemical entities (Fig. 2.27B). As demonstrated by the ^{31}P NMR stack plot, (*S*)-**22a** (96:4 er) is more rapidly acylated using (*S*)-BTM than with (*R*)-BTM. Using this method, we were able to assign absolute configurations for the α-hydroxy heteroaryl products obtained via CAHB/oxidation (Figure 2.27C). For example, the 3-substituted pyrrole derivative **22n** (99:1 er), synthesized via CAHB/oxidation using (*R*)-**B2**, undergoes more rapid (*S*)-BTM catalyzed acylation to yield **26n** (27% conversion in 12 h) compared to (*R*)-BTM catalyzed acylation (2% conversion in 12 h). The relative rates are consistent with predominant (*S*)-configuration of **22n**.

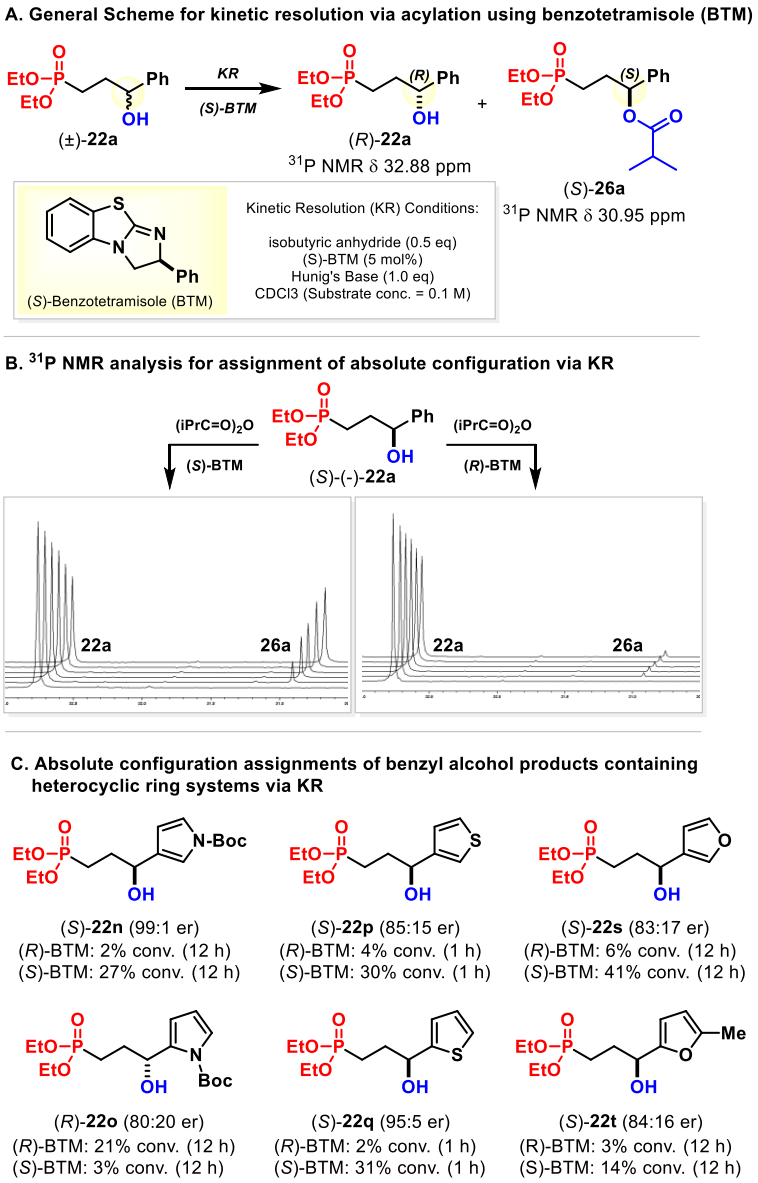


Figure 2.27. Stereochemical assignments based on kinetic resolution. (Adapted with permission from Ref. 16. Copyright 2019 The Royal Society of Chemistry)

In contrast to **22n**, the 2-pyrrole derivative **22o** (80:20 er), also prepared via CAHB/oxidation, undergoes relatively sluggish (*S*)-BTM catalyzed acylation to **26o** compared to (*R*)-BTM catalyzed acylation. The results indicate that predominantly (*R*)-**22o** is formed from 2-substituted pyrrole by CAHB with (*R*)-**B1**. We can only speculate that

the N-Boc moiety acts as an alternate directing group in the rhodium-catalyzed hydroboration thereby switching the sense of alkene π-facial selectivity. Although one might reasonably expect that 2-substituted thiophene and furan derivatives behave similarly, however, the data summarized in Figure 2.26 indicate that (*S*)-**22p-q** and (*S*)-**22s-t** are major stereoisomers formed via CAHB/oxidation. Thus, the sense of pi-facial selectivity is independent of the substitution nature of the substrates bearing heteroaromatic ring systems.

2.11. Summary

In this chapter, directed CAHB of allyl phosphonates bearing 1,1- and 1,2-disubstituted vinyl arenes was discussed. In case of the 1,1-disubstituted alkenes, CAHB leads to the formation of chiral tertiary boronic esters via regioselective β-boration. This result constitutes the first reported example of boron delivery to the more substituted carbon atom of an aryl substituted methylidene in the literature. Systematic studies of individual components of methylidene substrate **5a** suggested that the appropriate positioning of the phosphonate functionality and alkene conjugation are essential elements required for the observed regiochemistry. Mechanistic studies carried out using deuterium labelling experiments (CAHB using pinBD) suggested the migratory insertion of the C=C bond to a Rh-H/D bond forms a 3^{o}-alkyl rhodium intermediate which subsequently undergoes reductive elimination to form the tertiary boronic ester product. Substrates bearing meta and para substituents including halogen atoms undergo this reaction efficiently, yielding the corresponding tertiary boronic esters. Heteroaromatic substituents such as thienyl derivatives can be tolerated as well. The only limitation in the substrate scope is with ortho-

substituted aromatics where regioselective γ-boration leads to the formation of primary boronic esters.

The isomeric allyl phosphonates bearing 1,2-disubstituted vinyl arenes (*e.g.* **18a**) undergo efficient CAHB with regioselective γ-boration to form chiral secondary benzylic boronic esters. In these cases, isomeric *E* and *Z* substrates lead to the same major enantiomer of the chiral product formed. Mechanistic studies indicated rapid *Z* to *E* substrate isomerization occurring under reaction conditions leading to product stereoconvergence from any mixture of stereoisomeric substrates. A variety of substrates similar to **18a** were shown to undergo efficient CAHB, affording the corresponding γ-borated chiral secondary benzylic boronic ester products. Substrates bearing ortho-substituted aromatics did not change regiochemistry unlike in case of the 1,1-disubstituted vinyl arenes. Substrates bearing basic nitrogen functionality such as derivatives of aniline and substrates bearing common heteroaromatic ring systems of relevance in medicinal chemistry underwent efficient reaction, albeit with some unusual variations in regio- and enantioselectivity. Birman's chiral cyclic thiourea (benzotetramisole (BTM)) acylation catalyst was used to employ a kinetic resolution strategy for confirming the absolute configuration assignments for several of the chiral benzyl alcohol products derived from substrates bearing heteroaromatic ring systems.

2.12. References

(1) Corberán, R.; Mszar, N. W.; Hoveyda, A. H. "NHC-Cu-catalyzed enantioselective hydroboration of acyclic and exocyclic 1,1-disubstituted aryl alkenes" *Angew. Chem., Int. Ed.*, **2011**, *50*, 7079.

(2) Mazet, C.; Ge´rard, D. " Highly regio- and enantioselective catalytic asymmetric hydroboration of α-substituted styrenyl derivatives" *Chem. Commun.,* **2011**, *47*, 298.

(3) Zhang, L.; Zuo, Z.; Wan, X.; Huang, Z. "Cobalt-Catalyzed Enantioselective Hydroboration of 1,1-Disubstituted Aryl Alkenes" *J. Am. Chem. Soc.* **2014**, *136*, 15501.

(4) Zhang, H.; Lu, Z. "Dual-Stereocontrol Asymmetric Cobalt-Catalyzed Hydroboration of Sterically Hindered Styrenes" *ACS Catal.,* **2016**, *6*, 6596.

(5) Wang, Z.; He, X.; Zhang, R.; Zhang, G.; Xu, G.; Zhang, Q.; Xiong, T.; Zhang, Q. "Copper-Catalyzed Asymmetric Hydroboration of 1,1-Disubstituted Alkenes" *Org. Lett.* **2017**, *19*, 3067.

(6) Chakrabarty, S.; Takacs, J. M. "Phosphonate-Directed Catalytic Asymmetric Hydroboration: Delivery of Boron to the More Substituted Carbon, Leading to Chiral Tertiary Benzylic Boronic Esters" *ACS Catal.,* **2018**, *8*, 10530.

(7) Smith, S. M.; Hoang, G. L.; Pal, R.; Khaled, M. O. B.; Pelter, L. S. W.; Zeng, X. C.; Takacs, J. M. "γ-Selective directed catalytic asymmetric hydroboration of 1,1-disubstituted alkenes" *Chem. Commun.,* **2012**, *48*, 12180.

(8) Hoang, G. L.; Zhang, S.; Takacs, J. M. "Rhodium-catalyzed asymmetric hydroboration of γ,δ-unsaturated amide derivatives: δ-borylated amides" *Chem. Commun.,* **2018**, *54*, 4838.

(9) Shoba, V.; Takacs, J. M. "Remarkably Facile Borane-Promoted, Rhodium-Catalyzed Asymmetric Hydrogenation of Tri- and Tetrasubstituted Alkenes" *J. Am. Chem. Soc.*, **2017**, 139, 5740.

(10) Thacker, N. C.; Shoba, V. M.; Geis, A. E.; Takacs, J. M. "Surprisingly facile C–H activation in the course of oxime-directed catalytic asymmetric hydroboration" *Tet. Lett.*, **2015**, *56*, 3306.

(11) Smith, S. M., "Directed Catalytic Asymmetric Hydroboration (CAHB): An Effective Method For The Enantioselective Preparation Of Chiral Organoboronates" *dissertation, Ph.D.* **2012**, *University of Nebraska-Lincoln.*

(12) Fritschi, C. B.; Wernitz, S. M.; Vogels, C. M.; Shaver, M. P.; Decken, A.; Bell, A.; Westcott, S. A. "4,4,5,5-Tetraphenyl-1,3,2-dioxaborolane: A Bulky Borane for the Transition Metal Catalysed Hydroboration of Alkenes" *Eur. J. Inorg. Chem.* **2008**, *5*, 779.

(13) Wu, Z., Laffoon, S. D.; Nguyen, T. T.; McAlpin, J. D.; Hull, K. L. "Rhodium-Catalyzed Asymmetric Synthesis of β-Branched Amides" *Angew. Chem., Int. Ed.,* **2017**, *56*, 1371.

(14) Morrison, R. J.; Hoveyda, A. H. "γ-, Diastereo-, and Enantioselective Addition of MEMO-Substituted Allylboron Compounds to Aldimines Catalyzed by Organoboron-Ammonium Complexes" *Angew. Chem. Int. Ed.* **2018**, *57*, 11654.

(15) Noh, D.; Yoon, S. K.; Won, J.; Lee, J. Y.; Yun, J. "An Efficient Copper(I)-Catalyst System for the Asymmetric Hydroboration of β-Substituted Vinylarenes with Pinacolborane" *Chem.-Asian J.,* **2011**, 6, 1967.

(16) Chakrabarty, S.; Palencia, H.; Morton, M. D.; Carr, R. O.; Takacs, J. M. "Facile access to functionalized chiral secondary benzylic boronic esters via catalytic asymmetric hydroboration" *Chem. Sci.*, **2019**, *10*, 4854.

(17) Smith, S. M.; Takacs, J. M. "Amide-Directed Catalytic Asymmetric Hydroboration of Trisubstituted Alkenes" *J. Am. Chem. Soc.,* **2010**, *132*, 1740.

(18) Rhodium and iridium complexes are known to isomerize alkenes. For example, see (a) Morrill, T. C.; D'Souza, C. A. "Efficient Hydride-Assisted Isomerization of Alkenes via Rhodium Catalysis" *Organometallics*, **2003**, *22*, 1626; (b) Knapp, S. M. M.; Shaner, S. E.; Kim, D.; Shopov, D. Y.; Tendler, J. A.; Pudalov, D. M.; Chianese, A. R. "Mechanistic Studies of Alkene Isomerization Catalyzed by CCC-Pincer Complexes of Iridium" *Organometallics*, **2014**, *33*, 473; and the references cited therein.

(19) Douchet, H.; Fernandez, E.; Layzell, T. P.; Brown, J. M. " The Scope of Catalytic Asymmetric Hydroboration/Oxidation with Rhodium Complexes of 1,1′-(2-Diarylphosphino-1-naphthyl)isoquinolines" *Chem. Eur. J.* **1999**, *5*, 1320.

(20) Edwards, D. R.; Hleba, Y. B.; Lata, C. J.; Calhoun, L. A.; Crudden, C. M. "Regioselectivity of the rhodium-catalyzed hydroboration of vinyl arenes: electronic twists and mechanistic shifts" *Angew. Chem., Int. Ed.* **2007**, *46*, 7799.

(21) Birman, V. B.; Li, X. "Benzotetramisole: A Remarkably Enantioselective Acyl Transfer Catalyst" *Org. Lett.*, **2006**, *8*, 1351.

(22) Zhang, Y. H.; Xu, C. F.; Li, J. F.; Yuan, C. Y. "Candida rugosa Lipase-catalyzed Kinetic Resolution of Hydroxy-alkanephosphonates" *Chin. J. Chem.*, **2003**, *21*, 883.

CHAPTER THREE: PHOSPHONATE-DIRECTED CATALYTIC ASYMMETRIC HYDROBORATION OF TRISUBSTITUTED ALKENES

3.1. Review of reported examples of CAHB with trisubstituted alkenes

The use of trisubstituted alkenes as substrates for CAHB has historically proven challenging; few successful reports appear in the literature. In 2010, Smith and Takacs published the first successful report of efficient amide-directed CAHB of stereodefined trisubstituted alkenes (Figure 3.1A).[1] In the reported transformation, *E*- or *Z*- β,γ-unsaturated β,γ,γ-trisubstituted (which, giving numbering priority to the directing group, we sometimes refer to as a 1,2,2-trisubstituted) alkene substrates underwent efficient rhodium-catalyzed β-selective CAHB with pinacolborane to afford chiral secondary boronic esters. The highlight of this chemistry is the formation of two vicinal chiral centers assembled in a single step in a highly enantioselective reaction. For example, substrate (*Z*)-**27** underwent CAHB forming the chiral secondary boronic ester in excellent yield and high levels of stereoinduction to form (3*R*,4*R*)-**28** (83%, 97.5:2.5 er). The TADDOL-derived chiral cyclic phosphite (*R*,*R*)-**T1** was used as the ligand in this transformation.

In 2015, Tang and workers reported the CAHB of α-aryl enamides to afford α-amino chiral tertiary boronic esters (Figure 3.1B). Simple trisubstituted substrates such as. (*E*)-**29** were shown to undergo CAHB with the formation of the corresponding tertiary boronic ester product (*S*)-**30** (57%, 96.5:3.5 er) in high levels of enantioinduction. The monodentate phosphine ligand BI-DIME was used in a 1:1 ratio with a rhodium-precatalyst to generate the active catalyst in-situ.

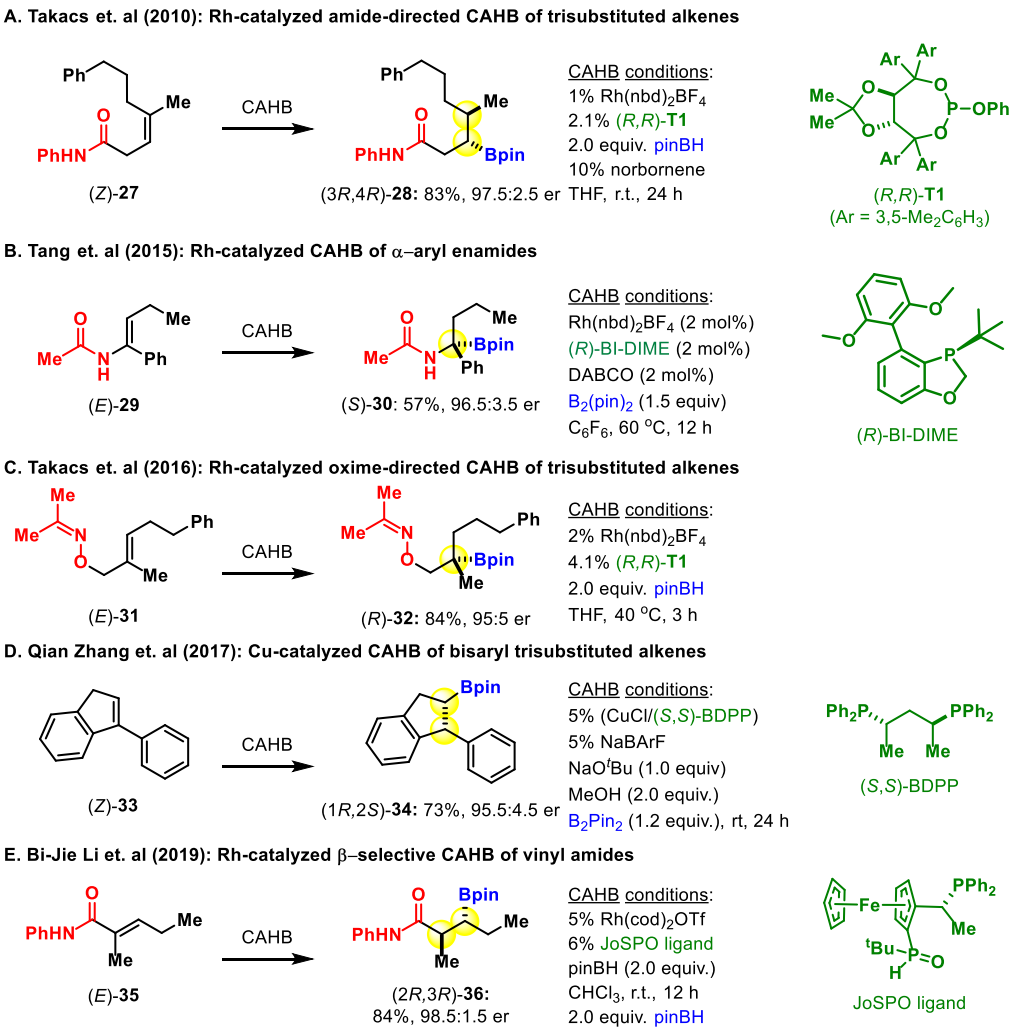


Figure 3.1. Reported examples of CAHB with trisubstituted alkenes.

In 2016, the Takacs group published a second report of efficient CAHB of stereodefined trisubstituted alkenes (Figure 3.1C).[2] In this report, an oxime-ether functionality was used as the directing group instead of the amide functionality used previously. A new alkene substitution pattern was also used in this study as compared to ones previously reported. *E*- or *Z*- β,γ-unsaturated β,β,γ-trisubstituted (*or* 1,1,2-trisubstituted) alkenes such as (*E*)-**31** underwent efficient oxime-directed β-selective CAHB with pinacolborane to afford novel chiral all-alkyl tertiary boronic ester (*R*)-**32**

(84%, 95:5 er) in excellent yield and high levels of enantioinduction. This work was the first example of a methodology to access chiral tertiary all-alkyl boronic esters via CAHB of trisubstituted alkenes. This methodology was also shown to be highly site-selective; in case of substrates bearing multiple alkenes, the alkene proximal to the directing group underwent selective reaction leaving the distal alkene untouched. The TADDOL-derived chiral cyclic phosphite (*R*,*R*)-**T1** was also used as the ligand in this transformation.

Subsequent examples of enantioselective B-H addition to alkenes appeared in the literature in the recent years. Some of these transformations (Figure 3.1 C-E) could be appropriately described as protoboration instead of hydroboration as no hydride source is involved in the processes. The postulated mechanism involve a copper-catalyst and diborane (B_2Pin_2) in the presence of an alkoxide base to generate a copper-boryl intermediate; the nucleophilic boron undergoes addition to an alkene resulting in an organo-copper intermediate bearing a boronic ester.[3] The organocopper intermediate subsequently undergoes protonolysis to release the copper catalyst and forms the C-H bond in the product. This mechanism is significantly different as compared to that generally postulated for a rhodium catalyst and a borane. A rhodium catalyst can undergo oxidative addition of a $X_2B–H$ bond resulting in a boryl-rhodium-hydride ($X_2B–Rh–H$) species which is assumed to be the active catalyst. Migratory insertion of the alkene into the Rh-H bond followed by reductive elimination of the C-B bond completes the catalytic cycle in rhodium catalysis.[4]

In 2017 Qian Zhang and coworkers reported examples of efficient protoboration of cyclic bisaryl trisubstituted alkenes via a copper-catalyzed transformation to afford chiral secondary boronic esters (Figure 3.1C).[5] For example, the substrate (*Z*)-**33** undergoes

efficient protoboration with boron-delivery at the less substituted terminus of the alkene to afford the chiral secondary benzylic boronic ester (1*R*,2*S*)-**34** (73%, 95.5:4.5 er). The bisphosphine ligand (*S*,*S*)-BDPP, which features a relatively small bite angle, was used in combination with a copper-precatalyst for optimal catalysis. Similar to Takacs' amide-directed CAHB of trisubstituted alkenes (Figure 3.1A), the key highlight of this work is the formation of two vicinal chiral centers generated in a single step with high levels oregio- and enantioselectivity. More examples of protoboration of trisubstituted alkenes to access chiral tertiary boronic esters are documented in Chapter 1 of this dissertation.

Recently, Bie-Jie Li and coworkers reported a β-selective CAHB of trisubstituted vinyl (*i.e.*, α,β-unsaturated) amide substrates (Figure 3.1E).[6] Li's work presents an unusual regiochemical outcome for such substrates. Vinyl amides have a strong substrate-controlled electronic bias towards formation α-boryl amides under rhodium-catalyzed CAHB conditions. This is typically explained by initial hydride addition at the β-position leading to a stable carbanion at the α-position of the amide. The formed α-boryl amide undergoes facile protodeboronation resulting in a net reduction of such substrates. The novelty of Li's work is in the identification of the highly electron rich bidentate ferrocene-based JoSPO ligand which results in switching the regioselectivity of the initial Rh-H addition to such substrates; the catalyst formed with the optimized ligand now leads to the initial hydride addition at the α-position of vinyl amide substrate leading to the formation of a β-Rh intermediate stabilized by the amide coordination. Subsequent C-B reductive elimination leads to boron delivery at the β-position. For example, the trisubstituted vinyl amide substrate (*E*)-**35** containing a trisubstituted alkene undergoes efficient protoboration with the delivery of boron at the β-position to afford chiral secondary boronic ester

(2*R*,3*R*)-**36** (84%, 98.5:1.5 er, >20:1 dr) in excellent yield and high levels of enantio- and diastereoselectivity. β-Borated products such as **36** are similar to ones obtained using Takacs' amide-directed β-selective CAHB of β,γ-di/trisubstituted alkene substrates. Apart from the unusual regiochemistry presented, Li's work also assembles two vicinal chiral centers in a single step and shows the possibility of accessing all 4-stereoisomers of products such as **36** using the methodology.

3.2. Phosphonate-directed CAHB of all-alkyl trisubstituted alkenes: access to all-alkyl substituted chiral tertiary boronic esters

In summer 2014 we started exploring the potential effectiveness of the phosphonate-functionality as a directing group for the CAHB of several classes of alkene substrates. This was at a time when there was a single reference[1] in the literature for the efficient CAHB of trisubstituted alkenes and the development of oxime-directed[2] CAHB of trisubstituted alkenes was just taking shape in the Takacs lab. Encouraged by the success of the amide- and oxime-ether directing groups and as part of the Takacs' group strategy to compare and contrast the results obtained using very different directing groups, we started exploring phosphonate-directed CAHB of stereodefined trisubstituted alkenes.

Allylic phosphonates bearing all-alkyl 1,1,2-trisubstituted alkenes were found to undergo highly efficient β-boration under standard CAHB conditions affording chiral tertiary boronic esters.[7] For example, substrate (*E*)-**37a** underwent efficient CAHB affording the chiral all-alkyl substituted tertiary boronic ester (*R*)-**38a** (82%, 99:1 er; Figure 3.2) in excellent yield and very high levels of enantioinduction. Substrate (*E*)-**37a** is similar to (*E*)-**29**, differing only in the nature of the directing group present (phosphonate vs. oxime

ether). Unlike the results obtained with conjugated methylidene substrates (*e.g.* substrates **3** *vs.* **5a**; see Chapter 2), the oxime- and phosphonate-functionalized trisubstituted alkene substrates (*i.e.*, **29** and **37**) undergo efficient CAHB with pinacolborane with similar regio and π-facial selectivity. For the phosphonate-directed reaction, the ligand (*R*,*R*)-**T2** bearing a 2-methylphenyl group at the terminus was found empirically to be superior to (*R*,*R*)-**T1**. Yields for phosphonate-directed CAHB are typically slightly higher (*ca.* 4-5%) using **T2** than those obtained using **T1**; the er of (*R*)-**38a** obtained using **T1** is 98.5:1.5.

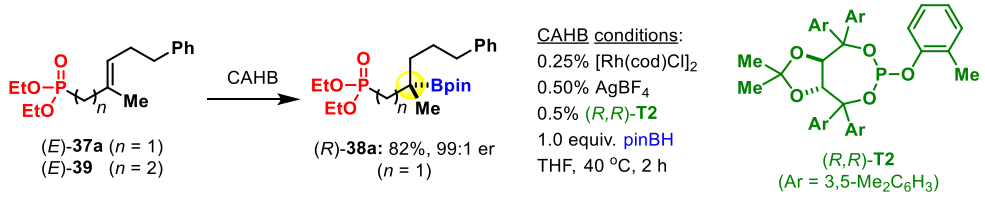


Figure 3.2. Phosphonate-directed CAHB of all-alkyl trisubstituted alkenes. (Adapted with permission from Ref. 7. Copyright 2017 American Chemical Society)

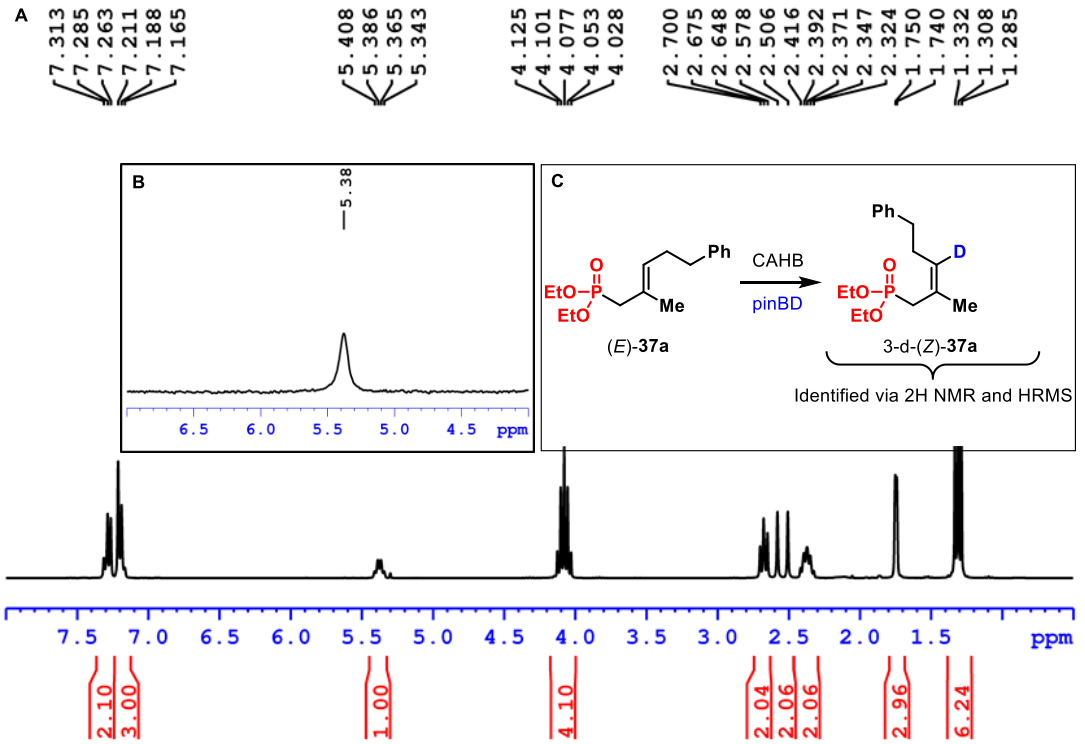
The formation of chiral, tertiary all-alkyl boronic esters is one of the novel features of this transformation. We estimate based on ^{31}P NMR analysis of the crude CAHB mixture that greater than >90% of the crude product is due to the major tertiary boronic ester. The remaining mass balance is accounted by 4-5 minor products. While we did not analyze any of the trace minor products, based on the results obtained with other substrates, we speculate the formation of alkene reduction product and the minor regioisomeric secondary boronic ester accounts for the majority of the remaining mass balance.

While the regioselectivity of the phosphonate-directed CAHB of all-alkyl trisubstituted alkenes (*e.g.* **38a**) is similar to those obtained with methylidene vinyl arene substrates (*e.g.* **5a**; See Chapter 2), an obvious question as to the origin of the unusual

regioselectivity remains. In the case of **5a**, we inferred that intermediacy of a tertiary benzyl-rhodium intermediate may be important in the catalytic cycle with methylidene vinyl arenes. The importance of the phosphonate-functionality in the CAHB of all-alkyl trisubstituted alkenes such as **38a** is obvious, given the lack of additional activation (*e.g.* presence of conjugation) and the unusual regioselectivity for generation of chiral tertiary boronic esters. As a result, we decided to check the reactivity of a one carbon homologue (**39**) under the standard conditions. In the event of CAHB, the substrate **39** is essentially unreactive, providing a direct evidence of the importance of the effective positioning of the phosphonate-functionality and the trisubstituted alkene for efficient catalysis.

3.3. Mechanistic insights into phosphonate directed CAHB of all-alkyl trisubstituted alkenes

As discussed in Chapter 2, deuterium labelling experiments can help shed significant light into the mechanism of a catalytic transformation. Deuterium labelling for substrate (*E*)-**37a** was carried out under standard CAHB conditions except for use of pinBD and the reaction quenched with methanol prior to completion to look for deuterium incorporation in substrate. The reaction of (*E*)-**37a** with pinBD using 2 mol% catalyst loading was quenched with methanol after 30 minutes and the reaction mixture was analyzed using ^{2}H NMR and HRMS. Deuterium incorporation was identified in the substrate as evidenced from ^{2}H NMR and the presence of the molecular ion peak corresponding to 3-*d*-(*Z*)-**37a** via ESI-HRMS (Figure 3.3).



D

Mass	RA	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
381.1600	100.00	381.1596	0.4	1.0	8.5	-1.$	n/a	1.#R	12C21 1H27 16O3 23Na 31P
		381.1583	1.7	4.5	21.5	-1.$	n/a	1.#R	12C29 13C 1H18 2H
		381.1619	-1.9	-5.0	17.5	-1.$	n/a	1.#R	12C28 1H22 23Na
		381.1620	-2.0	-5.2	11.5	-1.$	n/a	1.#R	12C23 1H26 16O3 31P
		381.1559	4.1	10.8	18.5	-1.$	n/a	1.#R	12C27 13C 1H19 2H 23Na
		381.1559	4.1	10.8	12.5	-1.$	n/a	1.#R	12C22 13C 1H23 2H 16O3 31P
		381.1643	-4.3	-11.3	20.5	-1.$	n/a	1.#R	12C30 1H21
		381.1535	6.5	17.1	9.5	-1.$	n/a	1.#R	12C20 13C 1H24 2H 16O3 23Na 31P
382.1637	22.02	382.1629	0.8	2.1	8.5	-1.$	n/a	1.#R	12C20 13C 1H27 16O3 23Na 31P
		382.1653	-1.6	-4.2	17.5	-1.$	n/a	1.#R	12C27 13C 1H22 23Na
		382.1653	-1.6	-4.2	11.5	-1.$	n/a	1.#R	12C22 13C 1H26 16O3 31P
		382.1658	-2.1	-5.5	8.5	-1.$	n/a	1.#R	12C21 1H26 2H 16O3 23Na 31P
		382.1677	-4.0	-10.5	20.5	-1.$	n/a	1.#R	12C29 13C 1H21
		382.1682	-4.5	-11.8	17.5	-1.$	n/a	1.#R	12C28 1H21 2H 23Na
		382.1682	-4.5	-11.8	11.5	-1.$	n/a	1.#R	12C23 1H25 2H 16O3 31P
		382.1706	-6.9	-18.1	20.5	-1.$	n/a	1.#R	12C30 1H20 2H

Figure 3.3. A. ^{1}H NMR of (*Z*)-**37a**. B. ^{2}H NMR (zoomed in to 4-7 ppm) after incomplete CAHB reaction with pinBD showing vinyl deuterium peak inferring the presence of 3-*d*-(*Z*)-**37a**. C. Deuterium incorporation in the vinyl position of (*E*)-**37a** seen during CAHB. D. HRMS data of CAHB mixture indicating presence of 3-*d*-(*Z*)-**37a** (highlighted in yellow).

The formation of 3-*d*-(*Z*)-**37a** is further indicated by the analysis of different levels of deuterium incorporation in (2*S*)-**40a** obtained via the CAHB of (*E*)-**37a** (obtained in a

separate experiment after complete substrate consumption) followed by oxidation (Figure 3.4). Formation of 3-*d*-(*Z*)-**37a** from (*E*)-**37a** under CAHB conditions generates an equivalent amount of pinBH (*vide infra*). The pinBH generated in-situ from substrate isomerization can react with (*E*)-**37a** followed by oxidation to afford the unlabeled proteo product (*S*)-**40a** after oxidation. The monodeuterated alcohol product 3-*d*-(2*S*)-**40a** can presumably arise via the CAHB of (*E*)-**37a** with pinBD followed by oxidation. Alternatively, a small amount of the diastereomeric 3-*d*-(2*S*)-**40a** product is also possible from the CAHB of 3-*d*-(*Z*)-**37a** with the pinBH generated in-situ from substrate isomerization followed by oxidation. The dideuterated product 3,3-d_2-(2*S*)-**40a** is also inferred in the product mixture. Its formation is possible via CAHB of (*E*)-**37a** with pinBD followed by oxidation.

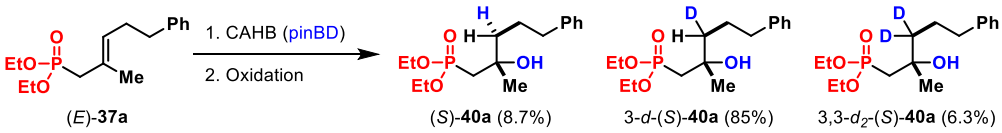


Figure 3.4. Different levels of deuterium incorporation seen in the CAHB of (*E*)-**37a** with pinBD (100% D purity) followed by oxidation. Note: Percentages inferred from ^{13}C NMR and HRMS.

The reaction between a Rh(I)-precursor ($Rh(nbd)_2BF_4$ *or* $[Rh(cod)Cl]_2/AgBF_4$) with the TADDOL derived chiral cyclic phosphite (*R*,*R*)-**T2** is used to generate the active CAHB catalyst in-situ. Figure 3.5 summarizes data obtained probing aspects of the nature of chiral rhodium catalyst used for the phosphonate-directed CAHB. The ligand-to-metal ratio (*i.e.*, **T2**:Rh) strongly influences the activity of the chiral catalyst. Graph A (Figure 3.5) compares the yield of **38a** over time for catalysts prepared with a 1:1 **T2**:Rh ratio (blue

line) and 2:1 **T2**:Rh ratio (red line). The catalyst formed using a 1:1 **T2**:Rh yields **38a** in about 80% yield after roughly an hour. The catalyst formed using a 2:1 **T2**:Rh ratio produces **38a** but in only 60% after roughly 4 hours. While the reaction is much slower, the enantiomer ratio of **38a** (99:1 er) is unchanged by the change in **T2**:Rh ratio. Graph B (Figure 3.5) shows the linear dependence of percentage enantiomeric excess (*ee*) of product **38a** on the enantiomeric purity of **T2**. The lack of a non-linear effect in this case is consistent with a 1:1 **T2**:Rh complex in the active catalyst. The results of this study indicate that a 1:1 ratio of ligand-to-metal combination is optimal for efficient catalysis. For the phosphonate-directed CAHB reactions, we routinely use a 1:1 **L**:Rh complex as the active catalyst.

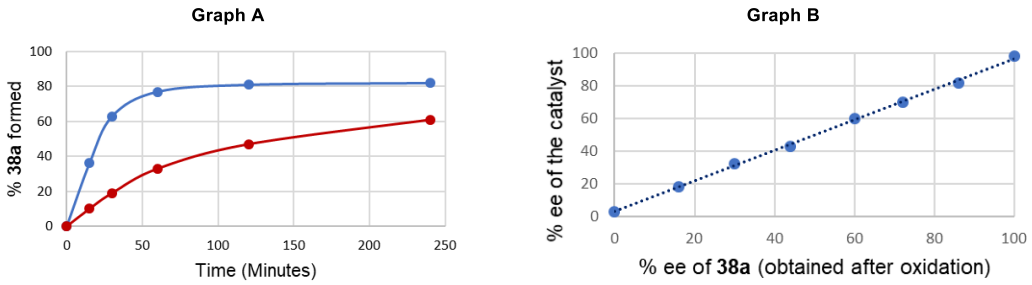


Figure 3.5. Key mechanistic considerations: Graph A compares the yield of **38a** over time for catalysts prepared using 1:1 (blue line) versus 2:1 (red line) **T2**:Rh ratios; Graph B plots percent ee of the product versus percent ee of the chiral catalyst. (Adapted with permission from Ref. 7. Copyright 2017 American Chemical Society).

The complexed rhodium catalyst is expected to undergo oxidative addition with pinBD, followed by migratory insertion of the alkene in substrate (*E*)-**37a** to the Rh-D bond resulting in Im-**1** (Figure 3.6) featuring a tertiary (3^o)-alkyl rhodium intermediate in the catalytic cycle. If this intermediate undergoes rapid rotation followed by β-H elimination,

then deuterium incorporation in the vinyl position is possible leading to 3-*d*-(*Z*)-**37a**. If the migratory insertion of the alkene into a Rh-B bond were to occur first, then it would lead to the formation of the CAHB product after C-D reductive elimination, and that wouldn't explain the formation of 3-*d*-(*Z*)-**37a**.

Therefore, formation of 3-*d*-(*Z*)-**37a** highlights several important aspects of the catalytic cycle that underlies the CAHB of (*E*)-**37a** (Figure 3.6): (i) alkene coordination to the rhodium complex is reversible. (ii) migratory insertion of the alkene into the Rh-H/D bond occurs first in a reversible fashion to form Im-**1**. (iii) rapid rotation followed by β-H elimination would lead to the formation of 3-*d*-(*Z*)-**37a** and the generation of an equivalent amount of pinBH in the reaction mixture which is available to react with (*E*)- or 3-*d*-(*Z*)-**37a** (*vide infra*). (iv) reductive elimination of the C-B bond completes the catalytic cycle. Essentially the mechanistic features are similar to those inferred for the methylidene vinyl arene substrate **5a**. However, while in case of **5a** there was additional stabilization because of the β-phenyl group (leading to the formation of a π-benzyl complex), the seemingly facile formation of a 3° alkyl rhodium intermediate from (*E*)-**37a** is unusual and is not easily rationalized.

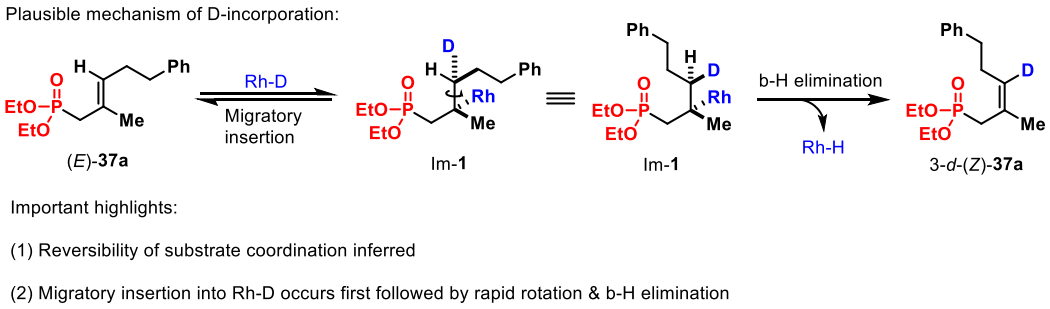


Figure 3.6. Plausible mechanism of deuterium incorporation in substrate (*E*)-**37a** under standard conditions with pinBD.

3.4. Substrate scope of phosphonate directed CAHB of all-alkyl trisubstituted alkenes[7]

The results obtained for a series of trialkyl substituted alkenes differing in the nature of the alkyl group at the γ-position (position labelled R^E) is summarized in Figure 3.7. Substrates similar to **37a** bearing substituted aromatics and heteroaromatics (*i.e.*, **37b-e**) undergo efficient β-selective CAHB, forming the corresponding chiral tertiary boronic esters. For example, the substrate bearing a 4-trifluoromethylphenyl unit (*i.e.*, **37b**) affords chiral tertiary boronic ester **38b** (78%, >99:1 er). The 4-chlorophenyl derivative **38c** (76%, 99:1 er), could in principle be used in subsequent cross-coupling chemistry,[8] further highlighting the potential of CAHB for generation of multifunctional synthons via CAHB. Furthermore, substrates **37d** and **37e** demonstrate that simple heteroaromatic ring systems can be carried through the CAHB sequence; chiral tertiary boronic esters **38d** (77%, 98.5:1.5 er) and **38e** (71%, 97:3 er) are obtained in good yields and high enantioselectivities.

Substrates bearing saturated alkyl substituents at the γ-position (*i.e.*, **37f** and **37g**) give tertiary boronic esters **38f** (83%, 97:3 er) and **38g** (80%, 98:2 er), respectively. The structurally related chiral substrate (2*E*,5*S*)-**37h** undergoes highly diastereoselective CAHB (>20:1 dr) with catalyst control; (*R*,*R*)-**T2** affords (2*R*,5*S*)-**38h** (83%), and (*S*,*S*)-**T2** affords the diastereomeric (2*S*,5*S*)-**38h** (82%). β-Borated products bearing a Boc-protected nitrogen substituent (**38i**) or hydroxy substituents protected as the benzoate (**38j**), benzyl ether (**38k**), or benzyloxymethyl ether (**38l**), are obtained with high levels of asymmetric induction. The chiral acetal substrate (2*E*,5*S*)-**37m** undergoes efficient CAHB, again with good catalyst control over diastereoselectivity. Depending on the configuration of the ligand **T2** used, either (2*R*,5*S*)-**38m** or (2*S*,5*S*)-**38m** is obtained in high yield (81-82%) and

in high levels of diastereoselectivity, 97:3 dr and 98:2 dr, respectively. The one carbon shorter analogue (2*E*,4*S*)-**37n** affords (2*R*,4*S*)-**38n** (51%, 91:9 dr) using (*R*,*R*)-**T2** but forms a rather complex mixture with (*S*,*S*)-**T2**. Substrates related to **37n**, bearing bulkier vinyl substituent at the γ-position such as in **37o** and **37p**, tend to react more sluggishly and give more side products; for example, lower yields are obtained for **38o** (52%, 90:10 er) and **38p** (53%, 98:2 er).

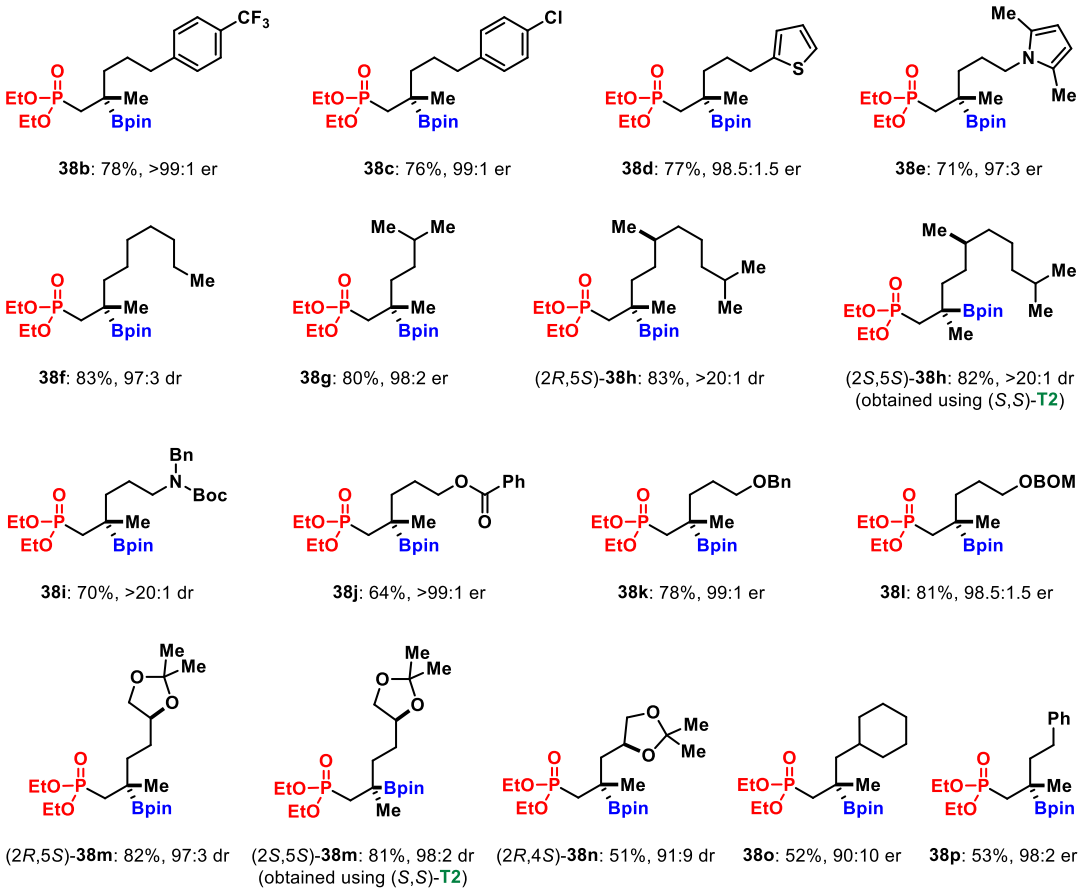


Figure 3.7. Substrate scope of phosphonate-directed CAHB of trialkyl substituted alkenes. CAHB conditions: 0.5 mol% Rh-precatalyst ($[Rh(cod)Cl]_2/2AgBF_4$), 0.5 mol% (*R*,*R*)-**T2** (unless otherwise indicated). In each case, the er is determined after oxidation to the corresponding tertiary alcohol or to other derivatives (See Chapter 5 for details). (Adapted with permission from Ref. 7. Copyright 2017 American Chemical Society).

The alkene geometry also plays a critical role in the reaction. For example, while (*E*)-**37a** undergoes CAHB/oxidation in high yield, (*Z*)-**37a** yields (*R*)-**38a** (40%, 99:1 er) in much lower yield but with high levels of enantioselectivity. The *re*/*si*-sense π-facial selectivity for CAHB of (*Z*)-**37a** is the same as that obtained from (*E*)-**38a**. Alkene reduction is a significant side reaction for substrate (*Z*)-**37a** accounting for the much lower yield obtained for the desired hydroboration product.

Figure 3.8 shows several substrates related to (*E*)-**37a** that gave poor results under the standard CAHB conditions. Attempted CAHB of substrate related to (*E*)-**37a** with a 1,2,2- substitution pattern (*e.g.* (*E*)-**37q**) results in essentially no reaction under the standard conditions. At this stage, we can only conclude this to be a limitation of the catalyst system generated using (*R*,*R*)-**T1**, because rigorous catalyst optimizations have not been carried out for this substrate. The substrate (2*E*,5*S*)-**37r** derived from (*S*)-citronellal was prepared to check for diastereoselective and site-selective reaction of the proximal alkene under standard CAHB conditions. In the event, however, the distal alkene partially undergoes competing reaction(s), and we were not successful in carrying out selective CAHB of just the proximal alkene. If the terminal alkene in (*S*)-citronellal was reduced using H_2/Pd-C prior to incorporation in substrate, for example in case of substrate (2*E*,5*S*)-**37h**; the latter undergoes efficient diastereoselective CAHB under standard conditions (Figure 3.7). The skipped diene substrate (*E*)-**37s** was prepared as part of our initial plan towards the synthesis of the natural product bakuchiol (See Chapter 4). Similar to the case of **37r**, the substrate **37s** did not undergo selective CAHB at the proximal alkene. The skipped distal alkene also underwent partial reaction under the standard CAHB conditions.

The substrate (*E*)-**37t** bearing a conjugated diene resulted in a complicated reaction mixture under the reaction conditions.

Another current limitation is found for bulkier analogs of substrates related to (*E*)-**37a**, wherein the methyl substituent on the alkene is replaced by bulkier substitutes. Such substrates tend to react sluggishly and resulted in complex reaction mixtures. For example, substitution of the vinyl methyl group in (*E*)-**37a** by an ethyl group as in (*E*)-**37u**, a benzyl group as in (*E*)-**37v** or the dimethyl allyl group as in (*E*)-**37w** did not result in clean transformations. A further complication arises in attempted isolation of the major product either at the boronate stage or post-oxidation to the corresponding alcohols for some of these substrates. In our hands, clean separation by chromatography on silica was not possible because the overall polarity of the molecules is dominated by the phosphonate functionality and changes in the hydrocarbon backbone did not provide sufficient differentiation for efficient separation of regioisomeric mixtures.

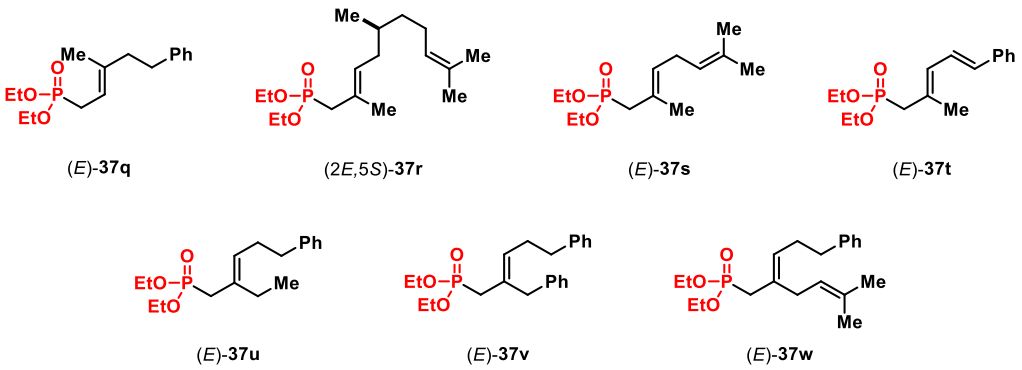


Figure 3.8. Limitations of the methodology: Unsuccessful trisubstituted substrates.

3.5. Phosphonate-directed CAHB of aryl-substituted (*i.e.*, styrenyl) trisubstituted alkenes: facile access to chiral tertiary benzylic boronic esters[9]

Figure 3.8 showed some limitations in substrate scope we uncovered for substrates related to (*E*)-**37a** under the standard CAHB conditions. Substitution of the β-vinyl methyl group to other bulkier substituents such as an ethyl group, benzyl group or a 3,3-dimethylallyl group resulted in substrates that were unsuccessful under the standard conditions. However, the substitution of the β-vinyl methyl group to a β-vinyl phenyl or aryl group resulted in substrates that underwent efficient β-selective CAHB. For example, substrate (*E*)-**41** undergoes efficient CAHB with pinacolborane using (*R*,*R*)-**T2**, generating the highly hindered chiral tertiary benzylic boronic ester (*R*)-**42** via delivery of boron to the more substituted carbon atom of the alkene undergoing the reaction (Figure 3.9). Comparison of the CAHB result of (*E*)-**41** with other substrates (**5a** and (*E*)-**37a**) that undergo conversion to tertiary boronic esters revealed an interesting disparity in the *re/si* sense of π-facial selectivity (Figure 3.9).

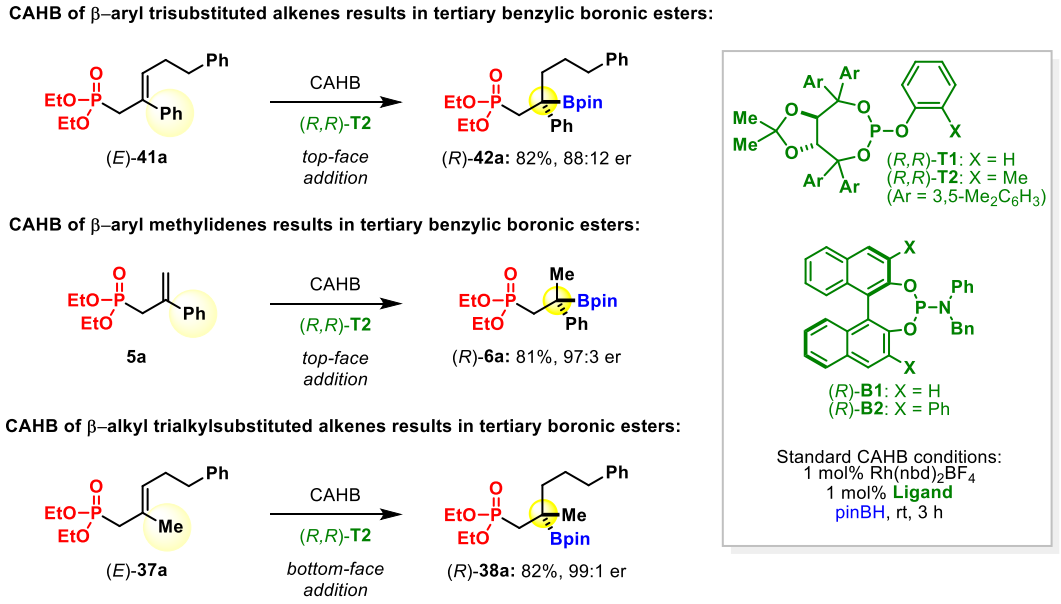


Figure 3.9. Disparity in π-facial selectivity in CAHB for substrates differing in the nature of the alkene substituent at the β-position.[9]

Using the same configuration of the ligand **T2**, substrates **5a**, (*E*)-**37a** and (*E*)-**41a** result in β-boration; however, the facial selectivity in the addition of pinBH across the π-system is dependent on the nature of the substituent appended at the β-position of the substrate. As illustrated in Figure 3.9, pinBH is added at the β-position from the "top-face" (of the perspective shown) for substrates **5a** and (*E*)-**41a** (bearing an aryl substituent at the β-position), whereas pinBH is added at the β-position from the "bottom-face" for substrate (*E*)-**37a** (bearing an alkyl substituent at the β-position) using (*R,R*)-**T2**. This reversal in π-facial selectivity may stem from π-stacking interactions between the substrate and the ligand for vinyl arene substrates or via involvement of the aromatic ring stabilizing a Rh-C intermediate. The latter argument has been long used to explain the regioselective hydroboration of simple vinyl arenes.[10] As a practical matter, however, the top/bottom sense of π-facial selectivity is of no consequence; either configuration of ligand **T2** is equally accessible, and hence either enantiomeric/diastereomeric products (in case of chiral substrates) can be prepared with equal facility.

3.6. Mechanistic insights into phosphonate directed CAHB of styrenyl trisubstituted alkenes

The CAHB results obtained from styrenyl trisubstituted alkenes (*e.g.* (*E*)-**41a**) are similar to those results obtained from all-alkyl trisubstituted alkenes (*e.g.* (*E*)-**37a**) and methylidene vinyl arene substrates (*e.g.* **5a**) in terms of the regiochemical outcome obtained. The only apparent difference is noted in terms of π-facial selectivity. We questioned whether the mechanism of CAHB with styrenyl trisubstituted alkenes is similar in terms of the sequence of elementary steps in the mechanistic cycle with the other two

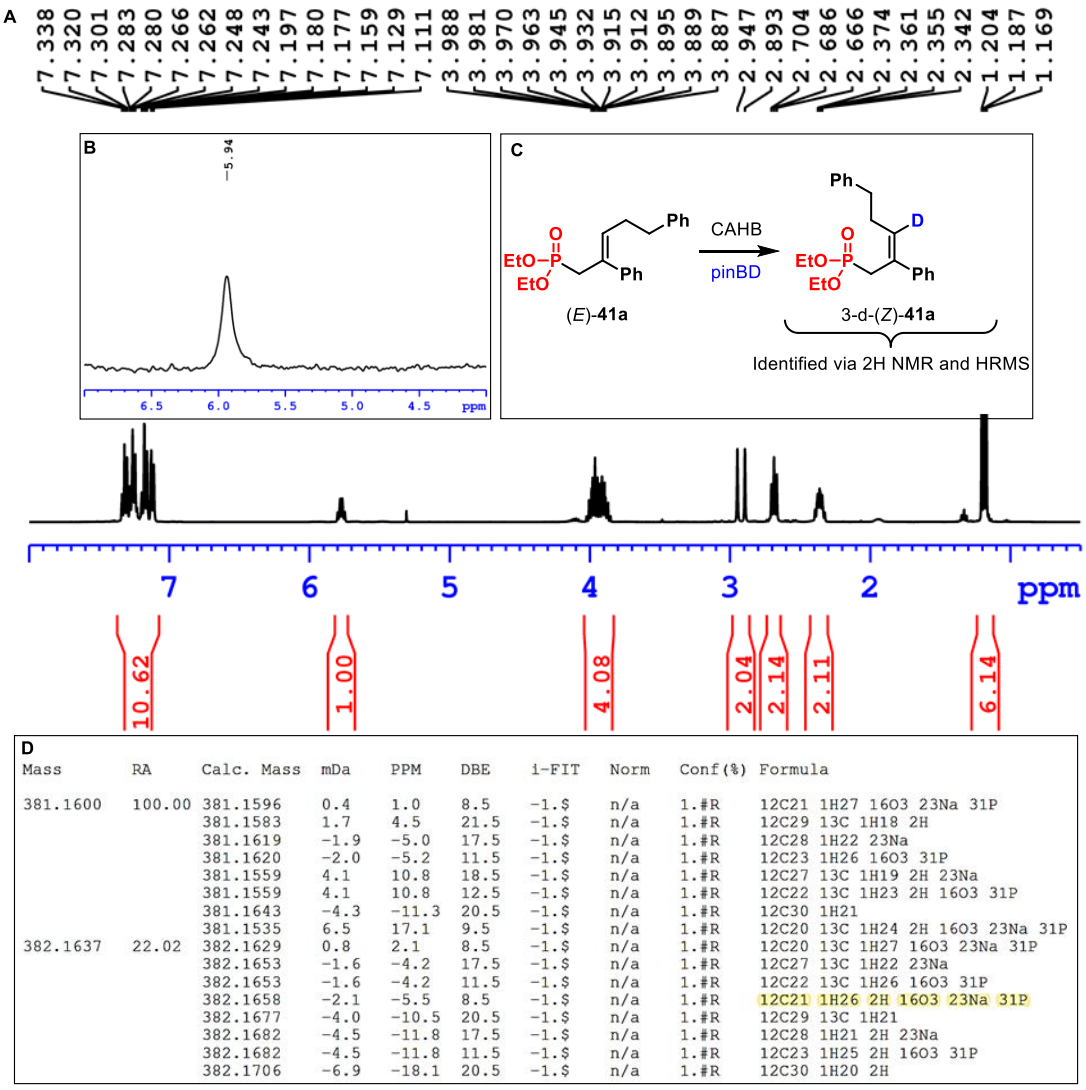


Figure 3.10. A. ^{1}H NMR of (*E*)-**41a**. B. ^{2}H NMR (zoomed in to 4-7 ppm) after incomplete CAHB reaction with pinBD showing vinyl deuterium peak inferring the presence of 3-*d*-(*Z*)-**41a**. C. Deuterium incorporation in the vinyl position of (*E*)-**41a** seen during CAHB. D. HRMS data of CAHB mixture indicating presence of 3-*d*-(*Z*)-**41a** (highlighted in yellow).

---

substrate types, or if it is any different. Deuterium labelling experiments carried out using pinBD under standard CAHB reaction conditions for substrate (*E*)-**41a** shows deuterium

incorporation in substrate under reaction conditions, a result similar to that observed for other substrates affording tertiary boronic esters (Figure 3.10).

Furthermore, the analysis of the tertiary alcohol product formed from (*E*)-**41a** via CAHB with pinBD followed by oxidation shows different levels of deuterium incorporation; the three different products identified are non-deuterated **43a**, the monodeuterated product 3-*d*-**43a** and the dideuterated product 3,3-d_2-**43a** (Figure 3.11). These results together indicate that the mechanism of CAHB of styrenyl trisubstituted alkenes (*e.g.* (*E*)-**41a**) is similar to that inferred for the other two classes of substrates. After oxidative addition of the Rh-complex with B–H/D bond, the substrate undergoes migratory insertion to the Rh–H/D bond forming a tertiary benzyl rhodium intermediate stabilized by chelation to the phosphonate. This intermediate could undergo C-B reductive elimination to form the mono-deutero product 3-*d*-**43a** and regenerate the catalyst, or it can undergo β-H elimination to incorporate deuterium in the alkene and form 3-*d*-(*Z*)-**41a**. In the event, a Rh–H intermediate is formed, interception of which by a substrate can explain the formation of the proteo product **43a** after oxidation. Similarly, migratory insertion of 3-*d*-(*Z*)-**41a** to the Rh-D bond followed by C-B reductive elimination can explain the formation of 3,3-d_2-**43a**.

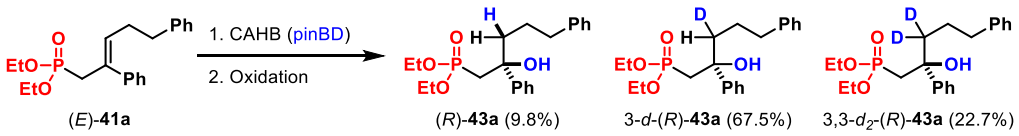


Figure 3.11. Different levels of deuterium incorporation seen in the CAHB of (*E*)-**41a** with pinBD (100% D purity) followed by oxidation. Note: Percentages inferred from ^{13}C NMR and HRMS.

3.7. Substrate scope of phosphonate-directed CAHB of styrenyl trisubstituted alkenes[9]

Figure 3.12 summarizes the effects of variations in several structural features of trisubstituted styrenyl substrates similar to (*E*)-**41a** on the overall outcome of CAHB: (1) the effect of ring size (5 *vs.* 6 membered ring) of the arene appended at the β-position, (2) the stereochemistry of the alkene (*E* vs. *Z* substrates), and (3) the presence of aryl substituents on both the carbon atoms of the alkene undergoing reaction. Substrate **41b** bears a 5-membered thiophene ring at the β-position and an alkyl chain bearing a chiral dioxolane at the γ-position. Catalyst controlled diastereoselective CAHB of both (*E*)- and (*Z*)-**41b** occurs with similar efficiency: β-boration leads to the formation of chiral tertiary benzylic boronic ester **42b** in excellent yield and high levels of stereoinduction. Use of (*R*,*R*)-**T2** results in (2*S*,5*S*)-**42b** (structure shown in Figure 3.10) and use of (*S*,*S*)-**T2** leads to the diastereomeric boronic ester (2*R*,5*S*)-**42b** from either diastereomer of **41b.** Thus, depending on the choice of the ligand used, either diastereomer of the boronic ester **42b** can be accessed with ease and the alkene stereochemistry does not impact overall yield or product diastereoselectivity. The chiral dioxolane unit appended at the γ-position is not a requirement for the reaction, however, its presence allows for the ease of diastereomer differentiation via ^{31}P NMR analysis of the crude CAHB mixture.

Substrates similar to **41b**, but bearing a 6-membered phenyl ring at the β-position (*e.g.* **41c**) in place of the five membered thiophene ring, exhibit more pronounced differences in CAHB results when diastereomeric (*E*)- and (*Z*)- stereoisomers were used. The trans-isomer (*E*)-**41c** undergoes CAHB with (*R*,*R*)-**T1** forming the tertiary benzylic boronic ester (2*R*,5*S*)-**42c** (80%, 91:9 dr) in excellent yield but in moderate levels of

diastereoselectivity as compared to the cis-isomer (*Z*)-**41b**. CAHB of (*E*)-**41c** with (*S,S*)-**T1** leads to formation of (2*S*,5*S*)-**42c** (78%, 85:15 dr) in high yields but with reduced levels of diastereoselectivity. However, the corresponding cis isomer (*Z*)-**41c** undergoes CAHB with much higher efficiency in terms of yield and diastereoinduction. CAHB using (*R,R*)-**T1** results in the formation of (2*R*,5*S*)-**42c** (83%, 96:4 dr) in excellent yield and diastereoselectivity. CAHB of (*Z*)-**41c** with (*S,S*)-**T1** leads to the formation of diastereomeric boronic ester (2*S*,5*S*)-**42c** (84%, 97:3 dr) in excellent efficiency as well. Thus, as compared to substrate **41b** (bearing a 5-membered thiophene ring at the β-position), the substrate **41c** bearing a 6-membered phenyl ring shows slight match/mismatched effect in the event of CAHB with enantiomeric chiral ligands used. Furthermore, while the alkene stereochemistry did not impact the overall yield and stereochemistry in case of substrate **41b**, the alkene stereochemistry in case of **41c** plays a crucial role in CAHB: the (*Z*)-substrate has superior performance as compared to the (*E*)-isomer.

In contrast to **41c**, substrate **41d** bears phenyl groups in both the β- and γ-positions, presenting a potential competition for regiocontrol. CAHB of β-aryl methylidene substrate **5a** results in preferential β-boration leading to chiral tertiary boronic esters such as **6a**, and CAHB of γ-aryl 1,2-disubstituted substrate **18a** results in preferential γ-boration leading to chiral secondary benzylic boronic esters such as **19a** (Chapter 2). The case of **41d** naturally raises the question as to which one of the two phenyl groups will determine the regiochemistry? In the event of CAHB with (*R,R*)-**T2**, (*E*)-**41d** yields the β-borated product (*R*)-**42d** (60%, 3:1 β:γ, 97:3 er) in moderate yield and regioselectivity yet in high levels of enantiocontrol. However, unlike the improved enantioselectivity seen for the (*Z*)- isomer

of **41c**, CAHB of diastereomeric (*Z*)-**41d** affords (*R*)-**42d** (71%, ~4:1 β:γ, 70:30 er) with a slightly improved yield but in much lower degree of enantioinduction. The presence of γ-phenyl group in (*Z*)-**41d** exerts a deleterious steric effect resulting in much lower levels of enantioinduction.

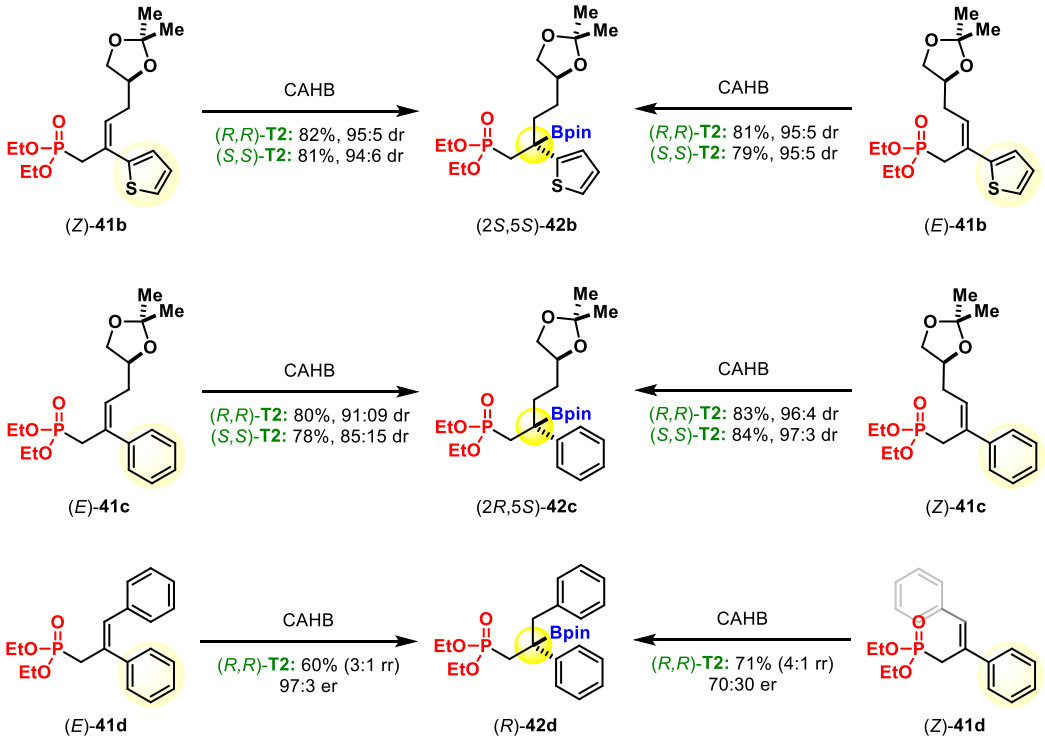


Figure 3.12. Phosphonate-directed CAHB of styrenyl trisubstituted alkenes: effect of ring size, alkene stereochemistry and the presence of aryl substituents in both carbon atoms of the alkene. (Adapted with permission from Ref. 9. Copyright 2018 American Chemical Society)

Substrates bearing a 2-thienyl moiety in the β-position as in **41b**, but with a simple alkyl substituent in the γ-position (*e.g.* **41e**), also undergo β-boration, yielding the corresponding tertiary benzylic boronic ester product (*S*)-**42e** (85%, 93:7 er) (Figure 3.13). The chiral substrate derived from citronellal (*i.e.*, **41f**) bears a pendant alkene as well a

remote stereocenter. It undergoes catalyst-controlled diastereo- and site-selective β-boration, leaving the distal alkene intact. CAHB of **41f** with (*R*,*R*)-**T2** affords (2*S*,5*S*)-**42f** (55%, 92:8 dr), and (*S*,*S*)-**T2** affords (2*R*,5*S*)-**42f** (58%, 92:8 dr). For substrate **41f**, a higher catalyst loading (2 mole percent) is used. However, even using the higher catalyst loading, the reaction of this substrate did not proceed to completion, perhaps due to the presence of multiple chelating sites in the substrate leading to catalyst deactivation. It is worth noting that while **41f** undergoes site selective CAHB of the proximal trisubstituted vinyl arene leaving the distal trialkyl substituted alkene untouched under the reaction conditions, the corresponding substrate bearing a methyl group at the β-position (compound **37r** shown in Figure 3.8) did not undergo selective CAHB. In case of **37r**, the distal alkene was also found to undergo competitive reaction, albeit not cleanly to a single product, even when using a limiting amount of pinBH. We speculate that the reactivity of the trisubstituted vinyl arene in case of **41f** is significantly higher and the directed CAHB leads to site-selective CAHB. However, in case of **37r**, while there is activation for the proximal alkene from that of the directing group, the distal alkene also underwent partial consumption because of the similar substitution pattern.

While substrates bearing a simple thiophene ring (*e.g.* **41b**) undergoes β-selective CAHB affording tertiary benzylic boronic esters in high yields and high levels of diastereoinduction, the corresponding substrates bearing extended ring aromatics such as the benzothiophene derivative (**41g**) undergoe CAHB with lesser efficiency. Diastereoselective CAHB of **41g** with (*R*,*R*)-**T2** leads to the formation of (2*S*,5*S*)-**42g** (68%, 92:8 dr), and CAHB with (*S*,*S*)-**T2** leads to the formation of (2*R*,5*S*)-**42g** (69%, 92:8 dr). The corresponding benzofuran derivative **41h** gives comparable results using (*R*,*R*)-

T2, affording (2*R*,5*S*)-**42h** (76%, 93:7 dr), but exhibits an unusual mismatched effect with (*S*,*S*)-**T2** to give (2*S*,5*S*)-**42h** (72%, 80:20 dr) with a much reduced level of diastereoselectivity.

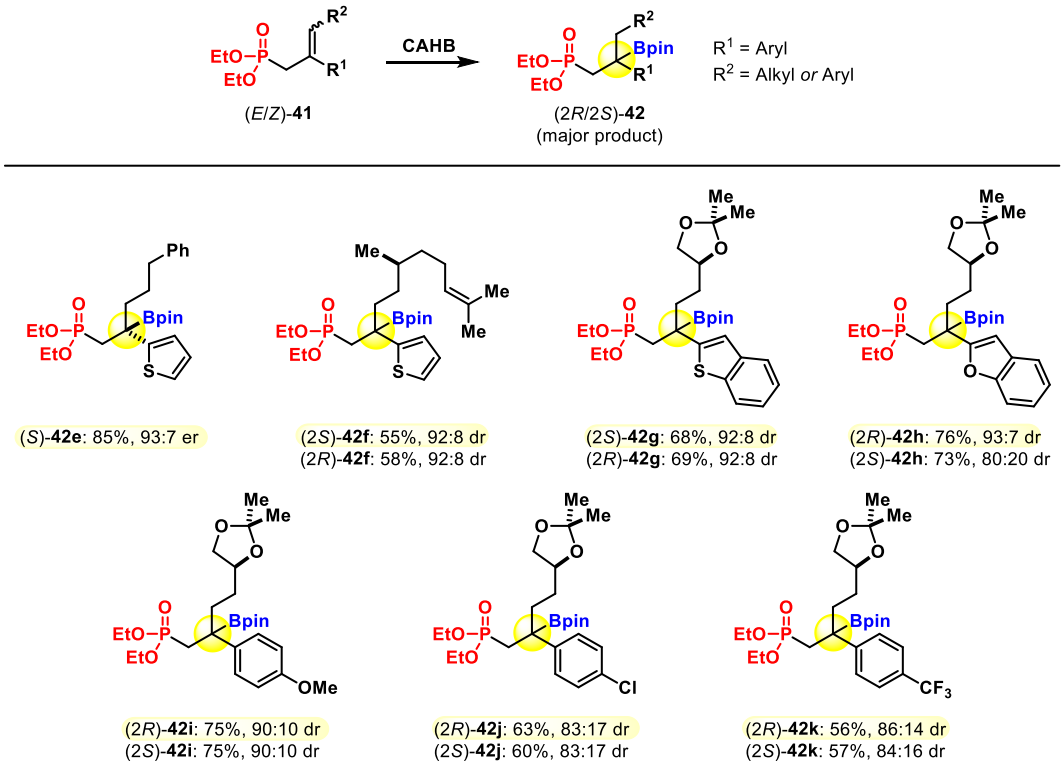


Figure 3.13. Substrate scope of phosphonate-directed CAHB of styrenyl trisubstituted alkenes. Note: Trans substrates were used. The *E*/*Z* descriptor of the substrate and the *R*/*S* descriptor of the chiral products is dependent on the nature of the β-substituent. Results highlighted in yellow are obtained using (*R*,*R*)-**T2**; nonhighlighted data are from reactions carried out using (*S*,*S*)-**T2**. (Adapted with permission from Ref. 9. Copyright 2018 American Chemical Society)

Finally, we find that allylic phosphonates bearing β-phenyl substituents, for example, (*E*)-**41i-k**, tend to undergo highly regioselective β-boration albeit with somewhat

lower diastereoselectivity. A significant electronic effect is also observed in this class of substituents. The 4-methoxyphenyl substrate **41i** behaves like the phenyl substituted substrate (*E*)-**41c**; either diastereomer of **42i** is formed with catalyst control in 75% yield but with modest diastereoselectivity (90:10 dr). However, presence of an electron-withdrawing substituent lowers the yield and diastereoselectivity. For example, substrates **41j** (4-chlorophenyl derivative) and **41k** (4-trifluoromethyl derivative) afford much lower yields (56-63%) of the corresponding chiral tertiary benzylic boronic esters **42j** (83:17 dr) and **42k** (*ca.* 85:15 dr), respectively.

3.8. Summary and conclusions from the studies of phosphonate-directed CAHB

In summary, enabling efficient access to chiral tertiary boronic esters via phosphonate-directed CAHB of several different alkene substrates including challenging trisubstituted alkenes, represents the key highlight of this dissertation work (Figure 3.14). Formation of chiral tertiary boronic esters via CAHB of trisubstituted alkenes was unprecedented in the literature until our group reported the first examples of oxime-[2] and phosphonate-directed[7,9] boration. Several new substrate types were also explored in the process such as trisubstituted styrenyl derivatives and bisaryl trisubstituted alkenes which underwent phosphonate-directed boron delivery at the more substituted carbon atom of the alkene undergoing reaction.

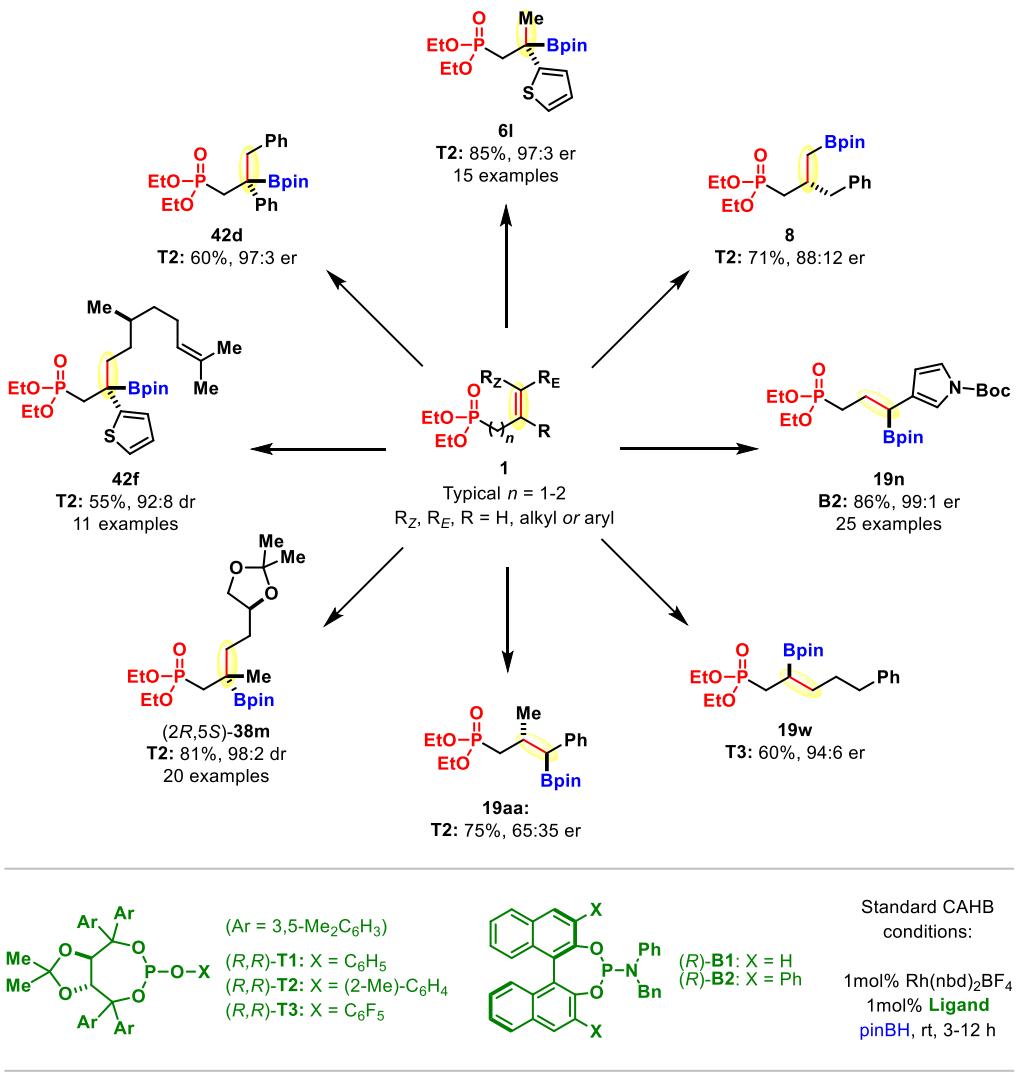


Figure 3.14. Summary of phosphonate-directed CAHB.

The mechanism of rhodium-catalyzed CAHB leading to formation of tertiary boronic esters is a subject of intellectual curiosity. Migratory insertion of the alkene to a Rh-H bond is generally accepted to be the first step in the mechanistic cycle.[11] However, we initially speculated that most likely our substrates were undergoing migratory insertion into a Rh-B bond first followed by reductive elimination of the C-H bond to form the tertiary boronic esters. While this speculation was not in lines with what is generally

accepted in the mechanistic cycle, we thought of the same to avoid invoking tertiary alkyl-rhodium intermediates in the mechanistic cycle. However, our deuterium labelling experiments for several of the substrates showed the reversibility of elementary steps in the mechanistic cycle, incorporation of deuterium in the vinyl position of the substrate and formation of dideuterated products. The data put together supports a mechanism consistent with migratory insertion of the alkene to the Rh-H bond occurring first to form a tertiary alkyl-rhodium intermediate, which undergoes C-B bond reductive elimination to form the chiral tertiary boronic ester product and complete the catalytic cycle. Deuterium labelling data also suggests that reductive elimination is likely the irreversible step in the catalytic cycle.

The outcomes from phosphonate-directed CAHB of different classes of alkene substrates is summarized in Figure 3.14. Tertiary boronic ester products such as **6l**, **38m**, **42f** and **42d** are obtained from the phosphonate-directed CAHB of β-aryl methylidene, β,γ-bisalkyl trisubstituted, β-aryl, γ-alkyl trisubstituted and β,γ-bisaryl trisubstituted alkene substrates respectively. The selectivity for the formation of chiral tertiary boronic esters from these substrate classes varied significantly. For example, the regioselectivity in CAHB of β-aryl methylidene substrates (*e.g.* **5l**) was at best about 4:1, however, very high levels of enantioinduction were generally achieved irrespective of the nature of the aryl group appended at the β-position. The only exception was in case of the substrate bearing a 3-thienyl group at the β-position (**5m**). CAHB of **5m** resulted in the tertiary boronic ester product **6m** (80%, 88:12 er) with a much-reduced level of enantioinduction. Several substrates in the class of all-alkyl trisubstituted alkenes (e.g. **37m**) underwent CAHB with high efficiency providing excellent yields and enantioinductions of the chiral boronic esters

formed. The major limitation in this class of substrates was the high levels of steric sensitivity. Replacement of the vinyl methyl group with larger alkyl groups resulted in non-selective reactions leading to mixtures of products that were not easily separated from each other.

The substrate class of β-aryl, γ-alkyl trisubstituted (*i.e.*,styrenyl trisubstituted alkenes, *e.g.* **41f**) underwent CAHB with high levels of selectivity yielding the corresponding tertiary boronic esters in high yields, however, the levels of enantioinductions were comparatively lower as compared to other substrate classes. The efficiency of enantioinduction was found to be dependent on (1) the alkene geometry for substrates bearing 6-membered aromatic ring at the β-position, with the *Z*-substrate resulting in higher levels of enantioinduction, (2) steric hindrance of extended ring systems such as benzothiophene/benzofuran resulted in lower levels of enantioinduction.

The substrate class of β,γ-bisaryl trisubstituted alkenes (*e.g.* **41d**) was a curious case. In the event of CAHB, boron is delivered to the carbon atom of the alkene proximal to the phosphonate-directing group resulting in the formation of tertiary boronic ester products. However, the regioisomeric ratio was much lower; about 3:1 ratio of regioisomers was obtained. The alkene geometry had a significant effect on the enantioinduction in this case with very low levels of enantioinduction obtained for the *Z*-substrate as compared to the *E*-counterpart.

1,2-disubstituted vinyl arene substrates (*e.g.* **18n**) are isomeric to the corresponding 1,1-disubstituted vinyl arene substrates (*e.g.* **5l**) and these result in the formation of chiral secondary benzylic boronic esters via regioselective γ-boration. High levels of selectivity were obtained in this substrate class and the limitations were seen with some common

heterocyclic ring systems of high relevance in medicinal chemistry. The allyl phosphonate substrates (*i.e.*, β,γ-unsaturated) substrates are generally more efficient as compared to the homoallyl phosphonate (*i.e.*, γ,δ-unsaturated) substrates. However, in case of the 1,2-disubstituted vinyl arene substrates, the corresponding homoallyl substrates also underwent CAHB with similar efficiency.

Several other permutations were tested which did not lead to successful results. Although, in principle, several of these systems could be further improved via ligand and borane optimizations. For example, the β-alkyl methylidene substrates (*e.g.* **7**) undergo CAHB with boron delivery to the less-substituted carbon atom of the alkene undergoing reaction leading to β-chiral primary boronic esters (*e.g.* **8**). β-alkyl, γ-aryl trisubstituted alkenes (*e.g.* **18aa**) undergo γ-selective CAHB resulting in chiral secondary benzylic boronic ester (**19aa**) with the formation of two vicinal chiral centers in a single step. However, with the common ligand systems used, we were at best able to get a very modest level of enantioinduction for **19aa** (**T2:** 75%, 65:35 er).

Phosphonate-directed CAHB of a variety of alkene substrates is presented in this dissertation. The reactions are carried out under ambient conditions, demonstrate a broad substrate scope and can be performed on multigram quantities. Because of the generality and practical significance of this methodology, we expect this work to add to a growing repertoire of methods to access functionized chiral secondary and tertiary boronic esters with high fidelity.

3.9. References

(1) Smith, S. M.; Takacs, J. M. "Amide-Directed Catalytic Asymmetric Hydroboration of Trisubstituted Alkenes" *J. Am. Chem. Soc.,* **2010**, *132*, 1740.

(2) Shoba, V. M.; Thacker, N. C.; Bochat, A. J.; Takacs, J. M. "Synthesis of Chiral Tertiary Boronic Esters by Oxime-Directed Catalytic Asymmetric Hydroboration", *Angew. Chem., Int. Ed.,* **2016**, *55*, 1465.

(3) Jarava-Barrera, C.; Parra, A.; López, A.; Crus-Acosta, F.; Collado-Sanz, D.; Cárdenas, D. J.; Tortosa, M. "Copper-Catalyzed Borylative Aromatization of p-Quinone Methides: Enantioselective Synthesis of Dibenzylic Boronates" *ACS Catal.,* **2016**, *6*, 442.

(4) Yang, Z.-D.; Pal, R.; Hoang, G. L.; Zeng, X. C.; Takacs, J. M. "Mechanistic Insights into Carbonyl-Directed Rhodium-Catalyzed Hydroboration: ab Initio Study of a Cyclic γ,δ-Unsaturated Amide" *ACS Catal.,* **2014**, *4*, 763.

(5) Wang, Z.; He, X.; Zhang, R.; Zhang, Ge.; Xu, G.; Zhang, Q.; Xiong, T.; Zhang, Q. " Copper-Catalyzed Asymmetric Hydroboration of 1,1-Disubstituted Alkenes" *Org. Lett.,* **2017**, *19*, 3067.

(6) Gao, T. T.; Zhang, W-W.; Sun, X.; Lu, H-X.; Li, B-J. "Stereodivergent Synthesis through Catalytic Asymmetric Reversed Hydroboration" *J. Am. Chem. Soc.,* **2019**, *141*, 4670.

(7) Chakrabarty, S.; Takacs, J. M. "Synthesis of Chiral Tertiary Boronic Esters: Phosphonate-Directed Catalytic Asymmetric Hydroboration of Trisubstituted Alkenes" *J. Am. Chem. Soc.,* **2017**, *139*, 6066.

(8) Vinogradova, E. V.; Fors, B. P.; Buchwald, S. L. "Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Triflates with Sodium Cyanate: A Practical Synthesis of Unsymmetrical Ureas" *J. Am. Chem. Soc.*, **2012**, *134*, 11132.

(9) Chakrabarty, S.; Takacs, J. M. "Phosphonate-Directed Catalytic Asymmetric Hydroboration: Delivery of Boron to the More Substituted Carbon, Leading to Chiral Tertiary Benzylic Boronic Esters" *ACS Catal.*, **2018**, *8*, 10530.

(10) Edwards, D. R.; Hleba, Y. B.; Lata, C. J.; Calhoun, L. A.; Crudden, C. M. "Regioselectivity of the Rhodium-Catalyzed Hydroboration of Vinyl Arenes: Electronic Twists and Mechanistic Shifts" *Angew. Chem., Int. Ed.* **2007**, *46*, 7799.

(11) Mannig, D.; Noth, H. "Catalytic Hydroboration with Rhodium Complexes", *Angew. Chem., Int. Ed.*, **1985**, *24*, 878.

CHAPTER FOUR: STEREOSPECIFIC TRANSFORMATIONS OF PHOSPHONATE-FUNCTIONALIZED CHIRAL SECONDARY AND TERTIARY BORONIC ESTERS

4.1. Stereospecific transformations of multifunctional chiral boronic esters

Chiral boronic esters are versatile intermediates in asymmetric synthesis because of the relative ease with which the C-B bond can be transformed into a myriad of rapidly evolving diverse stereospecific transformations.[1] In addition, chiral boronic esters and the corresponding chiral boronic acids are being increasingly seen as important therapeutic candidates as developments in efficient construction of chiral organoboronates continue to evolve.[2] Chiral boronic esters are highly bench stable and are stable to air and moisture, yet they undergo a variety of C-B bond substitutions upon appropriate activation via either (1) electrophile induced 1,2-migration from a boron-ate complex for stereoretentive transformations, or (2) S_E2 reaction between a boron-ate complex and an appropriate electrophile for stereoinvertive transformations.[3]

The Takacs group focuses on the synthesis of functionalized chiral boronic esters via directed CAHB of appropriately functionalized alkene substrates.[4] These multifunctional boronic esters can be converted to a variety of different targets of interest in medicinal chemistry by sequentially exploiting the chemistries of the boronic esters and that of the additional functionality present in the molecule (usually the directing group). For example, the *tert*-butyl carboxylic ester functionalized chiral primary boronic ester (*R*)-**45** (synthesized via ester-directed CAHB of methylidene substrate **44**) undergoes spontaneous lactonization under typical conditions employed for the oxidation of chiral boronic esters (H_2O_2/NaOH) to form β-benzyl substituted γ-lactone (*R*)-**46** (Figure 4.1).[4a]

β-Substituted butyrolactones such as compound **46** undergo diastereoselective alkylation and have been used in the synthesis of lignan natural products such as (+)-arctigenin.[5]

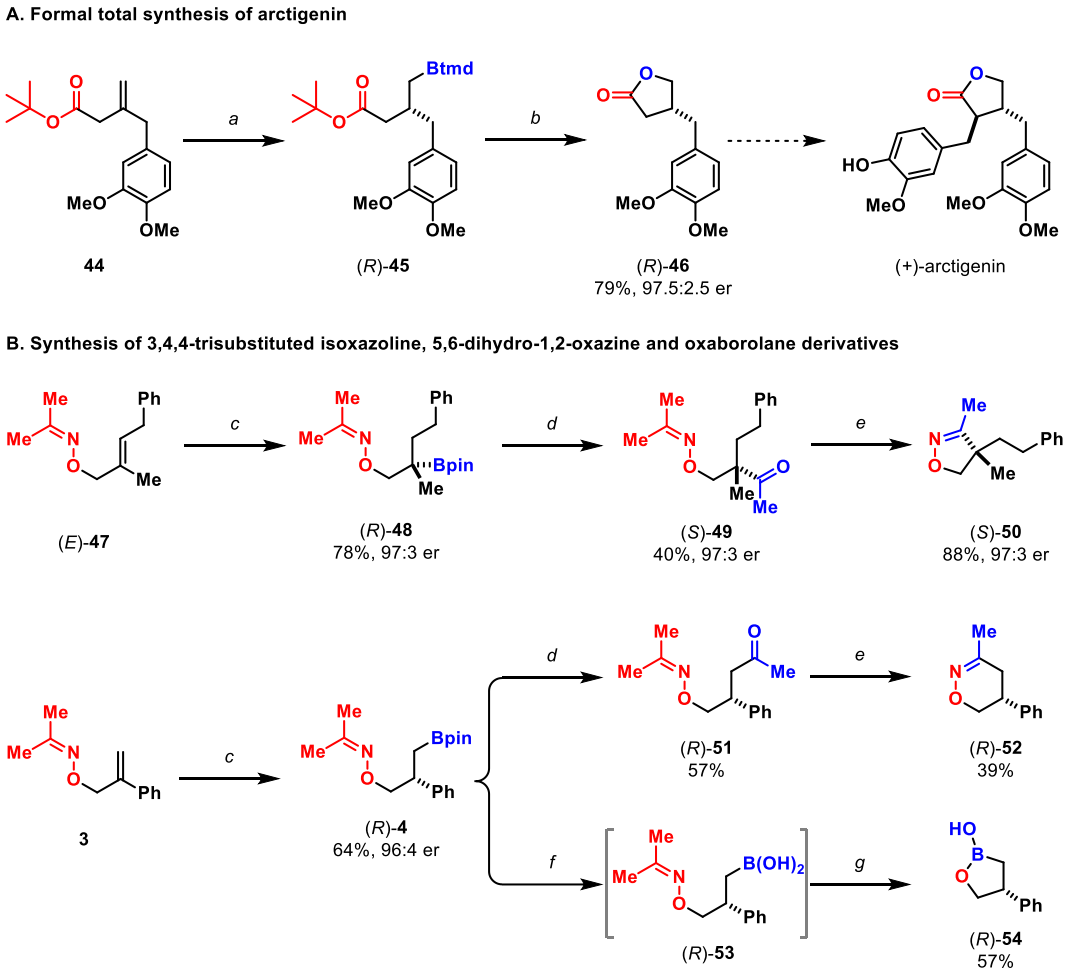


Figure 4.1. Transformations of multifunctional chiral boronic esters to obtain medicinally relevant synthetic targets. Reagents and conditions: (a) $Rh(nbd)_2BF_4$ (1 mol%), (*R*,*R*)-**T1** (2 mol%), tmdBH (2 equiv.), THF, 40 °C; (b) H_2O_2/NaOH; (c) $Rh(nbd)_2BF_4$ (1 mol%), (*R*,*R*)-**T1** (2 mol%), pinBH, THF, 40 °C; (d) i. $LiC(OEt)=CH_2$, -78 °C, THF. ii. I_2. iii. NaOMe, MeOH; (e) HCl, H_2O/MeOH, 40 °C; (f) BCl_3, DCM; (g) Raney Ni, H_2, MeOH/THF.

Other examples of using functionalized chiral boronic esters obtained via directed CAHB include transformations of oxime-ether functionalized chiral boronic esters to access unique structural motifs such as 4,4,5-trisubstituted isoxazoline, 5,6-dihydro-1,2-oxazine and oxaborolane derivatives (Figure 4.1B).[4c] Oxime-directed CAHB of trisubstituted alkene substrate (*E*)-**47** yields the chiral tertiary boronic ester (*R*)-**48** (78%, 97:3 er). Using conditions reported by Aggarwal et. al, Shoba and Takacs converted the chiral boronic ester (*R*)-**48** to the methyl ketone derivative (*S*)-**49** (40%, 97:3 er). Subsequent hydrolysis of the oxime-ether functionality generated the hydroxylamine intermediate which spontaneously undergoes condensation with the methyl ketone to generate the 3,4,4-trisubstituted isoxazoline derivative (*S*)-**50** (88%, 97:3 er). Chiral isoxazoline derivatives are found in several natural products and these exhibit diverse biological properties, however, the 3,4,4-trisubstituted chiral isoxazoline derivatives are not known in the literature. The synthesis of (*S*)-**50** by Shoba and Takacs constitutes the first report of enantioselective synthesis of a 3,4,4-trisubstituted isoxazoline.

The regioselective γ-boration of oxime-functionalized vinyl arene substrate **3** affords (*R*)-**4** (64%, 96:4 er).[4c] Using a similar strategy to that employed for the chiral tertiary boronic ester (*R*)-**48** en-route to the synthesis of 3,4,4-trisubstituted isoxazoline derivative (*S*)-**50**, the chiral primary boronic ester (*R*)-**4** was transformed to the methyl-ketone derivative (*R*)-**51** (57%) and its subsequent acid-catalyzed cyclization affords the chiral 5,6-dihydro-1,2-oxazine derivative (*R*)-**52** (39%).

Boron is fairly ubiquitous in earth's crust (8.6 x 10^{-4} %), occurring mainly as borates that serve structural roles as tetrahedral linker between four alkoxide units.[6] However, while organoboranes are versatile intermediates in asymmetric synthesis, they

are not found in nature. Recent developments in synthetic chemistry has allowed access to unique organoboron derivatives, some of which have promising activity in biological systems. For example, the oxaborolane Tavaborole (AN2690) is a topical drug for the treatment of onychomycosis.[7] However, chiral cyclic oxaborolane derivatives are not known in the present literature. The oxime-functionalized chiral primary boronic ester (*R*)-**4** was transformed to the chiral oxaborolane (*R*)-**54** by Bochat, Shoba and Takacs.[4e] Hydrolysis of the boronic ester in (*R*)-**4** using BCl_3 in dichloromethane gives the boronic acid (*R*)-**53** which upon treatment with Raney nickel results in N-O bond cleavage of the oxime-functionality and subsequent cyclization affords the chiral borocycle (*R*)-**54** (57%).

The syntheses of chiral heterocyclic compounds (*S*)-**50**, (*R*)-**52** and (*R*)-**54** highlight the potential utility of multifunctional chiral boronic esters for exploring unique chemical spaces in the context of medicinal chemistry, new molecular architectures and in the potential development of new drug candidates.

4.2. Stereospecific transformations of phosphonate-functionalized chiral tertiary benzylic boronic esters

Phosphonates and their corresponding phosphonic acids are often used as stable phosphate surrogates. The carbon-phosphorus bond (C-P) that defines these molecules is key to their potent bioactivity as well as their stability against enzymatic degradation.[8] Chiral phosphonates, particularly hydroxy- and amino-phosphonates are bioisosteres of the corresponding amino acids and are key structural elements found in antibiotics, antiviral and anticancer drugs.[9] However, the toolbox for introducing chirality via functionalization of phosphonates is largely limited to catalytic asymmetric hydrogenation of phosphonate-

functionalized alkenes.[10,11] The main goal towards exploration of the phosphonate-functionality as a directing group in CAHB of alkenes was to access phosphonate-functionalized chiral boronic esters and use these chiral synthons to access diverse chiral phosphonates via stereospecific C-B bond substitutions.

Phosphonate-directed CAHB of methylidene vinyl arenes such as **5a** and β-aryl trisubstituted alkenes such as **41a** result in preferential β-boration leading to formation of chiral tertiary benzylic boronic esters.[12] The reactivities of tertiary benzylic boronic esters (*e.g.* **6a**) are significantly different from those of tertiary alkyl-substituted boronic esters (*e.g.* **38a**). This is mainly because the presence of an aromatic ring appended to the chiral carbon significantly enhances the electrophilicity of the boron atom. As a result, while certain transformations such as protodeboronation,[13] occur readily with tertiary benzylic boronic esters, the corresponding reaction of trialkyl substituted boronic esters occurs only under forcing conditions and lead to non-stereospecific protodeboronation.[14]

Several common transformations of boronic esters were carried out using (*R*)-**6a** to demonstrate the potential utility of phosphonate-functionalized, chiral tertiary benzylic boronic esters (Figure 4.2). The chiral tertiary boronic ester is easily converted to the corresponding trifluoroborate salt (*R*)-**55** (87%) using KHF_2 in methanol;[15] trifluoroborate salts are generally more stable than the corresponding pinacol boronates and are of significant interest for metal-catalyzed cross coupling chemistry.[16] While there are several reports for efficient stereospecific-cross coupling reactions of chiral secondary trifluoroborate salts, there are no reports in the present literature for the stereospecific cross-couplings of chiral tertiary trifluoroborate salts. Morken's report on cross-coupling of tertiary trifluoroborate salts via radical mediated alkyl transfer[17] and Londregan's report

on construction of 1-heteroaryl-3-azabicyclo[3.1.0]hexanes by sp^3-sp^2 Suzuki-Miayura and Chan-Evans-Lam coupling reactions of tertiary trifluoroborates[18] are the only two reports of efficient cross-coupling of tertiary trifluoroborate salts in the present literature; but neither is stereospecific.

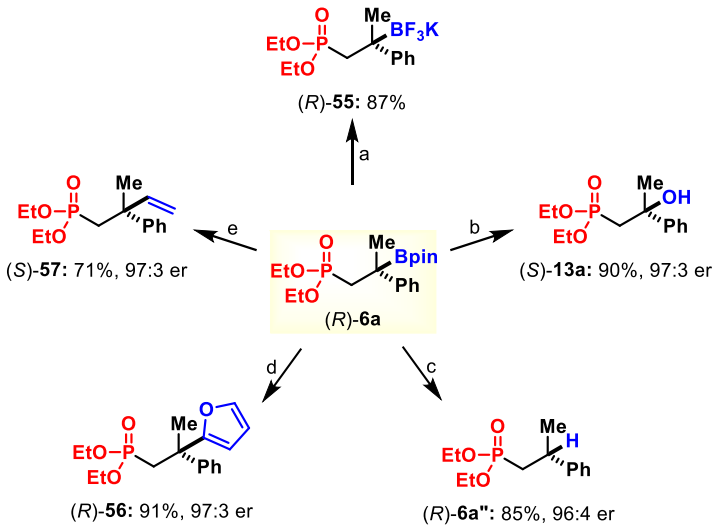


Figure 4.2. Synthetic utility of phosphonate-functionalized, chiral tertiary benzylic boronic esters is illustrated by selected transformations of **6a**. Reagents and conditions: (a) KHF_2, MeOH; (b) $NaBO_3.4H_2O$; (c) TBAF.H_2O; (d) (i) *n*BuLi, furan, -78 °C, THF; (ii) NBS; (iii) aq. $Na_2S_2O_3$; (e) (i) CH_2=CHMgBr; (ii) I_2; (iii) MeONa, MeOH. (Adapted with permission from Ref. 12. Copyright 2018 American Chemical Society)

Oxidation of (*R*)-**6a** by $NaBO_3.4H_2O$ affords the chiral tertiary benzyl alcohol (*S*)-**13a** (90%, 97:3 er). Protodeboronation[28] of **6a** using TBAF/H_2O yields the known chiral phosphonate (*R*)-**6a"** (85%, 96:4 er).[19] Cross-coupling of **6a** with 2-lithiofuran is highly efficient under the conditions reported by Aggarwal[14] to yield the furan derivative **56** (91%, 97:3 er) in high yield and essentially complete stereospecificity; the latter contains a quaternary carbon stereocenter bearing two aryl groups, a structural motif attracting recent

interest in medicinal chemistry.[20] Cross-coupling with vinylmagnesium bromide under similar conditions affords the vinyl derivative **57** (70%, 97:3 er).[15] These stereospecific C-B bond transformations construct chiral phosphonates bearing a quaternary chiral stereocenter. The Aggarwal cross-coupling procedures are successful in our system for coupling with 5-membered electron-rich furan and vinylation (synthesis of **56** and **57**); however, attempted cross-coupling with 6-membered ring aromatics using Aggarwal's procedure was not successful for the phosphonate-functionalized, chiral tertiary benzylic boronic ester **6a**.

4.3. Phosphonate-unmasking via oxophosphonate intermediates

As mentioned above, phosphonates and phosphonic acids are important constituents of bioactive compounds principally due to their capacity to act as stable phosphate surrogates by resisting hydrolysis.[8] In this section, the synthetic utility of the phosphonate moiety is highlighted by the chemistry of α-oxophosphonates (*i.e.*, acylphosphonates) (Figure 4.3). The common methods of preparing acylphosphonates are via the reaction of trialkylphosphite with an acid chloride,[21] a modification of the Michaelis-Arbuzov reaction, or via addition of a dialkylphosphite anion to an aldehyde followed by oxidation. The direct α-oxidation of phosphonates is not commonly employed in the literature, however, Weimer reported the oxidation of benzylic phosphonates to chiral α-hydroxyphosphonates by treatment of the phosphonate α-carbanion with camphorsulfonyl oxaziridine.[22] We used a similar strategy to oxidize phosphonate intermediates using 2-(phenylsulfonyl)-3-phenyloxaziridine (Davis' oxaziridine),[23] although our initial attempts to α-oxidize the boronic ester functionalized phosphonate **6a** were unsuccessful. Catalytic

hydrogenation of **57** gives **58**, which when treated with *n*BuLi and Davis' oxaziridine yields α-hydroxyphosphonate **59** (83%, 2:1 dr) in excellent yield but with minimal diastereoselectivity. However, the configuration of the α-chiral center is inconsequential because it is essentially lost in the subsequent steps.

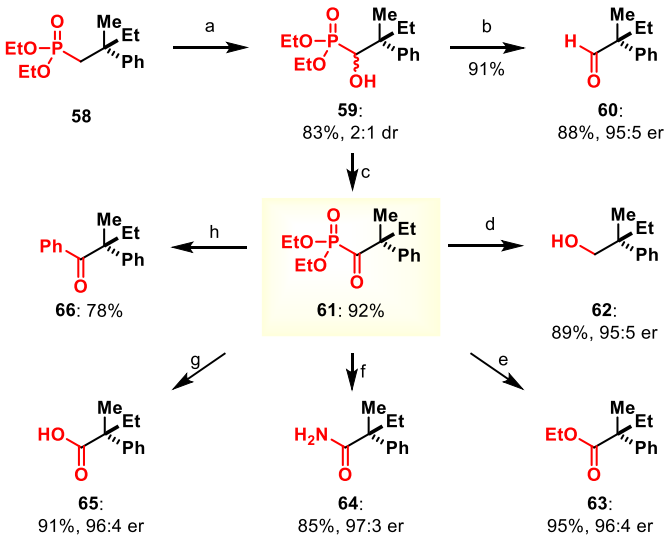


Figure 4.3. Oxidations leading to α-hydroxy- and oxophosphonates and their synthetic utility. Reagents and conditions: (a) *n*BuLi, –78 °C, THF; Davis' oxaziridine; (b) aq. $NaHCO_3$ reflux; (c) Dess-Martin Periodinane, CH_2Cl_2; (d) $LiAlH_4$, THF; (e) EtOH, DBU; (f) aq. NH_3, THF; cat. $(nBu)_4NBr$; (g) aq. NaOH; (h) (i) PhMgBr, –78 °C, THF; (ii) aq. NH_4Cl; (iii) aq. NaOH. (Adapted with permission from Ref. 12. Copyright 2018 American Chemical Society)

α-Hydroxyphosphonates such as **59** are aldehyde equivalents and these easily undergo elimination.[24] Thus, treating **59** with aqueous $NaHCO_3$ affords the chiral aldehyde (*S*)-**60** (88%, 95:5 er). Alternatively, oxidation of α-hydroxyphosphonate **59** with Dess-Martin periodinane affords acylphosphonate **61** (92%). Reduction of **61** with $LiAlH_4$ yields the known chiral alcohol (*S*)-**62** (89%, 95:5 er), confirming the absolute configuration

assigned to **6a**.[15,25] Acylphosphonates have also recently attracted interest as surrogates for esters and amides in asymmetric organocatalysis by serving the role of an active ester.[26] Thus, treatment of **61** with with (i) ethanol/DBU converts **61** to the chiral ester **63** (95%, 96:4 er), or (ii) aqueous ammonia affords the chiral amide (*S*)-**64** (85%, 97:3 er),[27] or (iii) aqueous sodium hydroxide forms the known chiral carboxylic acid[28] (*S*)-**65** (91%, 96:4 er).[29] Treatment of **61** with phenylmagnesium bromide gives after aqueous workup the stable α-hydroxyphosphonate as a mixture of diastereomers, the latter when treated with aqueous base liberates the known chiral phenyl ketone[30] (*S*)-**66** (78% overall yield).[31]

4.4. Stereoretentive and stereoinvertive transformations of phosphonate-functionalized chiral secondary benzylic boronic esters

While there are significant limitations, chiral tertiary boronic esters can be precursors to quaternary carbon stereocenters using the Aggarwal protocol for electrophile induced stereoretentive 1,2-B-to-C migration from an intermediate boron *"ate"* complex resulting in the net C-B to C-C bond substitution.[1] Chiral secondary boronic esters, on the other hand, are somewhat more versatile in terms of their utility. Chiral secondary boronic esters can also be elaborated via stereoretentive electrophile promoted 1,2-B-to-C migrations, stereoretentive palladium- and rhodium-catalyzed cross-coupling protocols and by stereoinvertive S_E2 reactions of boron-ate complexes with electrophiles.[1,3] For example, phosphonate-directed CAHB of 1,2-disubstituted vinyl arenes (*e.g.* (*E*/Z)-**18a**) affords functionalized chiral secondary benzylic boronic esters (*e.g.* (*S*)-**19a**). We demonstrated the synthetic utility of these phosphonate-functionalized, chiral secondary benzylic boronic

esters via stereoretentive and stereoinvertive C-B bond transformations of the boron-ate complex derived from (*S*)-**19a** (Figure 4.4).[32]

Stereoretentive cross-coupling with carbanions derived from electron rich vinyl and aromatic derivatives *via* electrophile-promoted 1,2-B-to-C migration of a boron-ate complex is generally quite facile under conditions reported by Aggarwal.[14,15] For instance, treatment of (*S*)-**19a** with excess vinyl magnesium bromide followed by I_2 and sodium methoxide affords the vinyl derivative (*R*)-**67** (79%, 95:5 er) in high levels of stereospecificity.[15] Similarly, reaction of (*S*)-**19a** with 2-lithiobenzofuran followed by NBS affords the *gem*-bisaryl product (*S*)-**68** (68%, 96:4 er) with essentially complete enantiospecificity.[14] While cross-coupling with 2-lithiobenzofuran is facile with the secondary benzylic boronic ester (*S*)-**19a**, the analogous transformation does not work with the tertiary benzylic boronic ester (*R*)-**6a**. Attempted cross- coupling of (*R*)-**6a** with 2-lithiobenzofuran results essentially in complete protodeboronation resulting in the formation of **6a"**, however, the reaction with 2-lithiofuran works efficiently (Figure 4.2). This was a common problem encountered in several attempted C-B bond transformations with phosphonate-functionalized chiral tertiary benzylic boronic esters. If the electrophile induced 1,2-B-to-C migration is not fast enough (For mechanism, see Figure 1.25), protodeboronation of the ate-complex perhaps due to adventitious moisture or during aqueous workup leads to the reduced product.

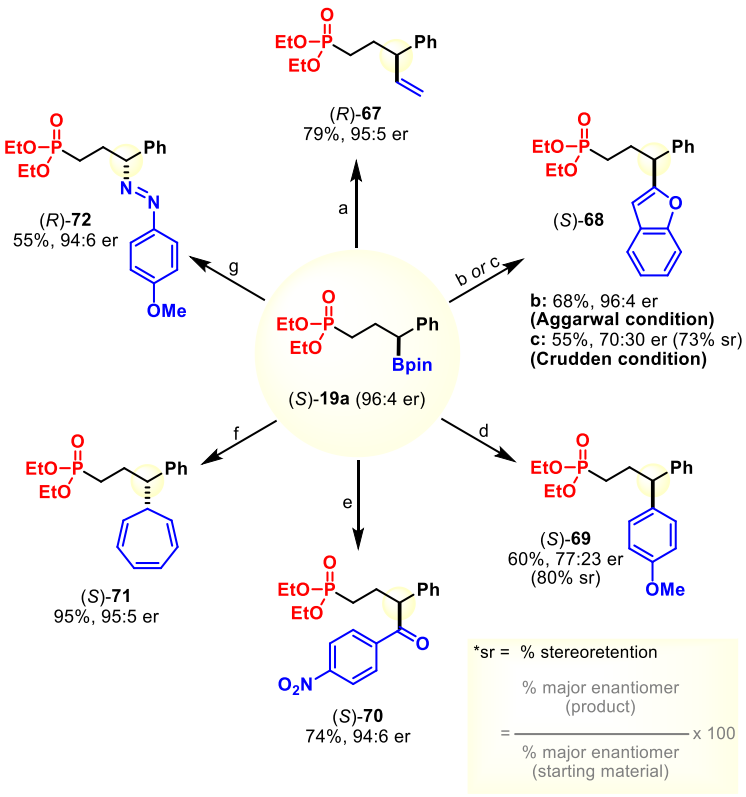


Figure 4.4. Synthetic utility of chiral secondary benzylic boronic esters illustrated by stereoretentive and stereoinvertive C-B bond transformations. Reagents and conditions: (a) (i) Excess CH_2=CHMgBr, THF, -78 ^oC to rt; (ii) I_2/MeOH, -78 ^oC; (iii) NaOMe/MeOH; (iv) $Na_2S_2O_3$ (aq.); (b) (i) benzofuran-2-yllithium, THF, -78 ^oC; (ii) NBS, THF, -78 ^oC; (iii) $Na_2S_2SO_3$ (aq.); (c) 2-iodobenzofuran, Ag_2O, $Pd_2(dba)_3$/PPh_3, THF, 60 ^oC; (d) 4-iodoanisole, Ag_2O, $Pd_2(dba)_3$/PPh_3, THF, 60 ^oC; (e) (i) 4-nitrobenzaldehyde, $[Rh(cod)Cl]_2$, KHF_2, dioxane/H_2O ; (ii) TEMPO, TCCA, CH_2Cl_2; (f) (i) (3,5-bis(trifluoromethyl)phenyl)lithium, THF, -78 ^oC to -40 ^oC; (ii) Cycloheptatrienyl tetrafluoroborate, rt.; (iii) $NaHCO_3$ (aq); (g) (i) (3,5-bis(trifluoromethyl)phenyl)lithium, THF, -78 ^oC to -40 ^oC; (ii) 4-Methoxybenzenediazonium tetrafluoroborate, 0 ^oC; (iii) $NaHCO_3$ (aq.). (Adapted with permission from Ref. 32. Copyright 2019 The Royal Society of Chemistry).

The stereoselective palladium-catalyzed cross-coupling of chiral boronic esters has attracted recent interest both due to its synthetic utility and the interesting mechanistic issues raised by the potential for either stereoretention[33] or stereoinversion[34]; the outcome is often found to be dependent upon the participation or non-participation of polar substituents present in the substrate.[35,36] For example, Hall (**110a**),[34a,34c] Biscoe (**110b**),[34b] Suginome (**110c**)[34d,34f] and Molander (**110d**)[34e] independently reported functionalized chiral secondary boronic esters that underwent palladium-catalyzed cross coupling reactions with stereoinversion (Figure 4.5A). The inversion in stereochemistry is usually rationalized by the intramolecular coordination of the polar substituents to the boron atom; this intramolecular coordination leads to invertive transmetallation resulting in overall inversion of stereochemistry of the cross-coupling product. Several other examples are reported by Morken (**110e**),[33a] Suginome (**110f**)[33b] and Takacs (**110g-h**)[4b,4d] wherein cross-coupling proceeds with stereoretention. Morken reported that **110e** undergoes hydroxyl-directed inner-sphere stereoretentive transmetallation in the course of palladium-catalyzed cross-coupling reaction. Suginome's cyclic aminoboronate **110f** also undergoes an overall stereoretentive cross-coupling reaction with palladium. In the examples published by Takacs, stereoretention occurs presumably because the coordinating functionality is not present in proximity to the organoboron derivative undergoing the reaction (Figure 4.5B).

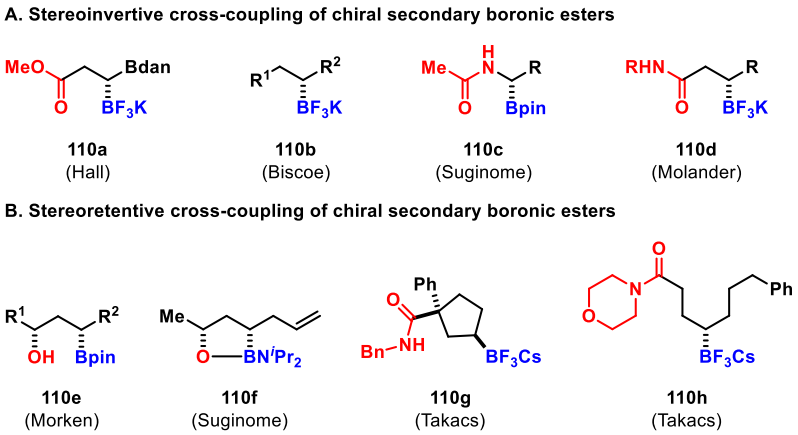


Figure 4.5: Stereochemical course of Suzuki-Miaura cross-coupling reactions of chiral secondary organoboron derivatives. A: Stereoinvertive cross-coupling of chiral secondary boronic esters. B: Stereoretentive cross-coupling of chiral secondary boronic esters. (Adapted from Ref. 4d Copyright 2017 The Royal Society of Chemistry).

Chiral secondary benzylic boronic esters are rather unique in the context of palladium-catalyzed cross-coupling because of their high propensity to undergo protodeboronation. Only the protocol recently introduced by Crudden is reportedly effective in favoring C-C coupling versus protodeboronation.[37] The degree of stereoretention (sr; See definition in Figure 4.4) varies, but in favorable constructs, Crudden reports that it proceeds with 84-94% sr. While Crudden's protocol is highly cited in the literature, few applications of the method have thus far been reported. The outcome for the bifunctional substrate (*S*)-**19a** (96:4 er) was, therefore, uncertain. Cross-coupling of (*S*)-**19a** with 2-iodobenzofuran under Crudden's conditions [$Pd_2(dba)_3$/PPh_3/Ag_2O] gives (*S*)-**68** (55%, 70:30 er, 73% sr); cross-coupling proceeds with predominant stereoretention (as evidenced by matching the HPLC traces of **68** obtained using Aggarwal's electrophile-induced stereoretentive 1,2-B-to-C migration; See chapter 5 for experimental details and

HPLC traces). However, the reaction proceeds with significant erosion of enantiopurity. Similarly, cross coupling of (*S*)-**19a** with 4-iodoanisole yields (*S*)-**69** (60%, 77:23 er, 80% sr). In spite of the moderate level of stereochemical integrity, the result is useful. We were unable to prepare **69** via the 1,2-B-to-C migration protocol. This again illustrates a limitation of Aggarwal's 1,2-B-to-C migration; the transformation works well for 5-membered aromatic rings, but fails with 6-membered aromatic rings in our functionalized chiral boronic esters.

An alternative rhodium-catalyzed cross-coupling procedure also developed by Aggarwal effects the stereoretentive addition of chiral trifluoroborate salts to electron-deficient aromatic aldehydes or other non-enolizable aldehydes (For mechanism, see Figure 1.24).[38] A modification of this original procedure developed by Aggarwal was reported by Tang and co-workers wherein the trifluoroborate salt is generated in-situ by addition of aqueous KHF_2 solution.[39] Following Tang's modification of Aggarwal's original procedure, (*S*)-**19a** underwent efficient Rh-catalyzed stereoretentive addition to 4-nitrobenzaldehyde to afford the aryl ketone (*S*)-**70** (74%, 94:6 er) after oxidation; the latter cross-coupling proceeds with only slight erosion of enantiopurity over two steps.

Chiral secondary boronic esters are known to undergo several stereoinvertive C-B bond transformations with strong electrophiles via an S_E2 mechanism.[3,48] For example, the intermediate boron-ate complex formed by addition of (3,5-bis(trifluoromethylphenyl) lithium to (*S*)-**19a** (96:4 er) readily reacts with cycloheptatrienyl tetrafluoroborate to effect the net C-B to C-C bond substitution to give (*S*)-**71** (95%, 95:5 er) in excellent yield and stereochemical purity. Similarly, the net stereoinvertive C-B to C-N bond substitution is accomplished by treating the *in-situ* generated boron-ate complex with 4-

methoxybenzenediazonium tetrafluoroborate to give the diazo compound (*R*)-**72** (55%, 94:6 er). The diazo compound **72** is highly light and heat sensitive. It undergoes spontaneous decomposition in chloroform within minutes, however, proved stable in dichloromethane, methanol and isopropanol.

4.5. Stereospecific transformations of phosphonate-functionalized chiral alkyl substituted tertiary boronic esters

Phosphonate-directed CAHB of trialkyl substituted alkenes (*e.g.* **37a**) results in efficient access to chiral alkyl-substituted tertiary boronic esters (*e.g.* **38a**).[40] The reactivities of chiral all-alkyl tertiary boronic esters are significantly different from chiral benzylic boronic esters. The latter are more reactive as the electrophilicity of the boron is significantly enhanced by the presence of an aromatic ring. Figure 4.6 illustrates the stereospecific transformations we have carried out for the chiral tertiary all-alkyl substituted boronic ester (*R*)-**38a**; these include its conversion to β- and γ-hydroxyphosphonates and aminophosphonates and to phosphonates bearing a quaternary all-carbon stereocenter. The latter are common structural motifs found in bioactive natural products and pharmaceutical drugs and yet often pose a significant challenge for their synthesis.[41]

The CAHB reaction of (*E*)-**37a** has been carried out on a gram scale using 0.5% catalyst loading using the ligand (*R*,*R*)-**T2** and pinacolborane to afford (*R*)-**38a** (82%, 99:1 er). Oxidation of (*R*)-**38a** using $NaBO_3.4H_2O$ yields the chiral, tertiary β-hydroxyphosphonate (*S*)-**40a** (95%, 99:1 er). Cross-coupling reactions of (*R*)-**38a** under

conditions reported by Aggarwal and coworkers are facile and afford the furan derivative (*R*)-**73a** (71%)[42] and the vinylated derivative (*R*)-**74a** (93%).[43] Attempts to convert **4a**

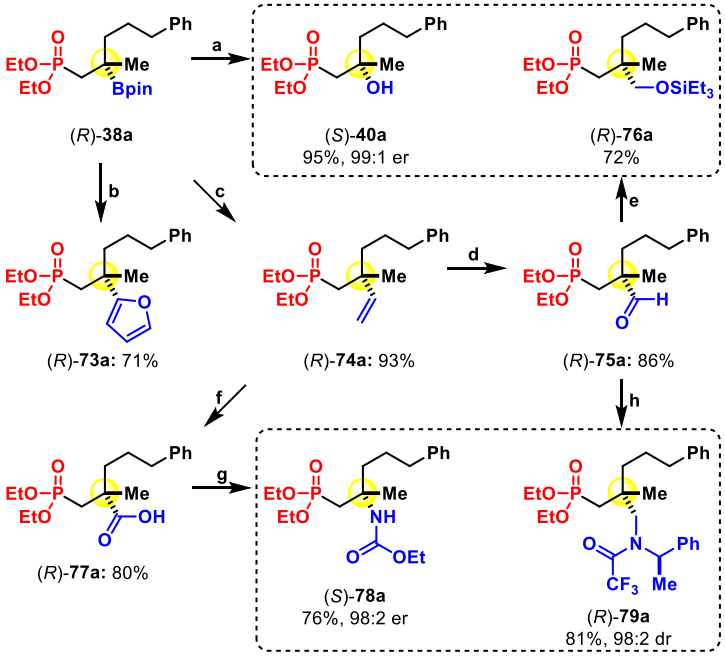


Figure 4.6. Utility of phosphonate functionalized chiral alkyl-substituted tertiary boronic esters is illustrated by selected transformations of (*R*)-**38a**. Reagents and conditions: (a) $NaBO_3.4H_2O$; (b) (i) *n*BuLi, furan, -78 °C, THF; (ii) NBS; (iii) aq. $Na_2S_2O_3$; (c) (i) CH_2=CHMgBr, THF; (ii) I_2, MeOH; (iii) MeONa, MeOH; (d) (i) O_3, CH_2Cl_2, 0 °C; (ii) Et_3N, rt; (e) Et_3SiH, [Ru(*p*-cymene)Cl_2]$_2$, toluene, 50 °C; (f) (i) O_3, CH_2Cl_2, 0 °C; (ii) Et_3N; (iii) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*BuOH, rt; (g) (i) DPPA, toluene reflux; (ii) EtOH; (h) (i) (*R*)-(+)-*α*-methylbenzylamine, AcOH, $NaCNBH_3$; (ii) $(CF_3CO)_2O$, Et_3N, THF, rt. (Adapted with permission from Ref. 40. Copyright 2017 American Chemical Society)

directly to the latent aldehyde or carboxylic acid moieties using the typical conditions employed for boronic esters were not successful.[15] Such transformations require in-situ generation of either dichloromethyllithium or bromomethyllithium by treatment of the mixture of boronic ester and dichloromethane/dibromomethane with *n*BuLi. Since the α-hydrogens of phosphonates are somewhat acidic (pKa ~ 30-35), competing deprotonation results in competing side reactions leading to complex reaction mixtures. We devised an indirect way to carry out the one-carbon homologation to the corresponding aldehyde.

Ozonolysis of the vinyl derivative (*R*)-**74a** followed by a mild reductive workup[44] yields the chiral phosphonoaldehyde (*R*)-**75a** (86%). With the aldehyde in hand, ruthenium-catalyzed reductive silylation affords the silyl protected chiral γ-hydroxyphosphonate (*R*)-**76a** (72%).[45] Reductive amination[46] of (*R*)-**75a** with (*R*)-(+)-α-methylbenzylamine followed by acylation affords the chiral γ-aminophosphonate (*R*)-**79a** (76% over two steps, 98:2 dr). Acylation using trifluoroacetic anhydride was crucial as the acylated derivative allowed for the determination of diastereomeric excess via ^{31}P as well as ^{19}F NMRs. The diastereomers of γ-aminophosphonate without acylation (**93a**; see Chapter 5) did not resolve in ^{31}P NMR.

Attempts to convert **38a** directly to chiral, tertiary β-aminophosphonate[10] using several commonly employed methods[47] for the direct C-B to C-N bond transformation were unsuccessful. This is mainly because direct C-B to C-N bond transformation usually requires transformation of a boronic ester to a strongly electrophilic dichloro-organoboron intermediate which undergoes ate-complex formation with an azide prior to undergoing the 1,2-migration. However, generation of the electrophilic dichloro-organoboron species is carried out via either (1) treatment of pinacolboronates with excess BCl_3,[4b] or (2) treatment

of a trifluoroborate salt with excess $SiCl_4$ to effect R-BCl_2 formation via σ-bond metathesis.[19] The usage of such strong Lewis acids lead to functional group incompatibility issues, and phosphonates are not stable under these reaction conditions. Morken's amination protocol involving lithiated methoxyamine as the nucleophile was known to be unsuccessful for tertiary boronic esters.[19b] We, therefore, developed an alternate way to transform the C-B bond of our phosphonate-functionalized, chiral tertiary boronic ester to a C-N bond. Ozonolysis of vinylated intermediate (*R*)-**74a** followed by Lindgren/Pinnick oxidation[48] affords the chiral carboxylic acid (*R*)-**77a** (80%). Its conversion to the chiral β-aminophosphonate (*S*)-**78a** (76%, 98:2 er) via Curtius rearrangement[49] occurred smoothly under the standard conditions.

4.6. Formal total synthesis of the cytotoxic natural product (*S*)-(+)-bakuchiol

In addition to their potential as pharmacophores for medicinal chemistry, phosphonates enable other useful synthetic transformations. For example, the Horner-Wadsworth-Emmons olefination involves stable α-carbanions derived from phosphonates functionalized with electron-withdrawing groups appended at the α-position (*e.g.* -COOR, -CN etc.). While C-B bond functionalization from phosphonate-functionalized chiral boronic esters allows for the synthesis of diverse chiral phosphonates, sequential utilization of the boronic ester functionality and the phosphonate functionality in the formal total synthesis of the cytotoxic natural product (*S*)-(+)-bakuchiol[50] further illustrates the synthetic utility of these chiral phosphonate-functionalized, chiral tertiary boronic esters (Figure 4.7).[12] (*S*)-(+)-Bakuchiol possess a remote alkene as well as a challenging skipped diene subunit in which the two alkene moieties are separated by a quaternary all-carbon

stereocenter. We envisioned utilizing the chemistry of the boronic ester and the phosphonate in **38x** sequentially to form the skipped diene subunit at a late stage in the synthetic sequence.

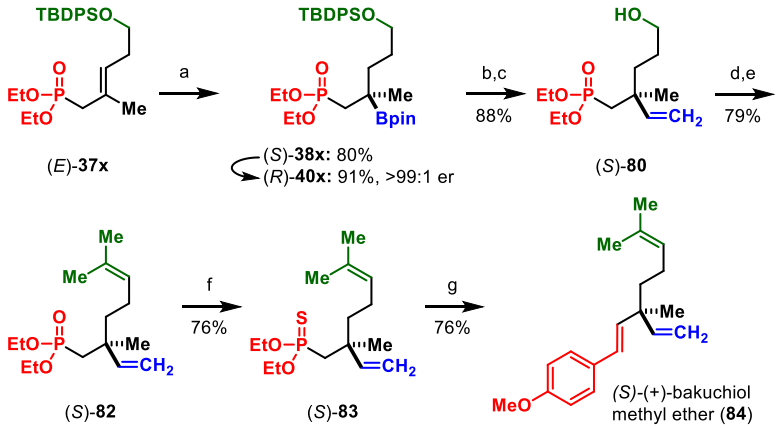


Figure 4.7. Formal total synthesis of (*S*)-(+)-Bakuchiol. Reagents and conditions: (a) $[Rh(cod)Cl]_2$ (0.25 mol%), $AgBF_4$ (0.50 mol%), (*S*,*S*)-**T2** (0.50 mol%), pinBH (1.1 equiv.), THF (*c* = 1M), rt, 12 h; (b) (i) CH_2=CHMgBr, THF, -78 ^oC; (ii) I_2, MeOH, -78 ^oC; (iii) NaOMe, MeOH; (iv) $Na_2S_2O_3$ (*aq.*); (c) TBAF, H_2O; (d) DMSO, $Py.SO_3$, Hünig's base; (e) $(CH_3)_2CH=PPh_3$; (f) Lawesson's reagent, toluene reflux; (g) *n*BuLi, 4-methoxy-benzaldehyde. (Adapted with permission from Ref. 40. Copyright 2017 American Chemical Society)

CAHB of (*E*)-**37x** with (*S*,*S*)-**T2** affords (*S*)-**38x** (80% on a gram scale); the enantioselectivity (>99:1) is determined after oxidation to the tertiary alcohol (*R*)-**40x**. Cross-coupling of (*S*)-**38x** with vinylmagnesium bromide[15] followed by deprotection of the silyl ether yields (*S*)-**80**. Oxidation to the terminal alcohol to the corresponding aldehyde using a modified Swern oxidation (Parikh-Doering oxidation;[51] DMSO, $Py.SO_3$) followed by Wittig olefination to (*S*)-**82** sets the stage for exploiting the phosphonate-functionality

to complete the synthesis. Direct phosphonate olefination is limited in scope since β-hydroxy phosphonates lacking electron withdrawing substituents at the α-position do not undergo elimination without activation.[52] However, Corey found that β-hydroxy thiophosphonates readily undergo elimination to form alkenes.[53] Treating phosphonate **82** with Lawesson's reagent[54] affords thiophosphonate **83**. Deprotonation of **83** by *n*BuLi followed by the addition of 4-methoxybenzaldehyde smoothly yields (*S*)-(+)-bakuchiol methyl ether (**84**).[55] Conversion of **84** to the natural product was previously reported.[22b] Since either enantiomer of the chiral monophosphite **T2** is equally accessible, a sequence beginning with (*R,R*)-**T2** was carried out to give the enantiomeric (*R*)-(-)-Bakuchiol methyl ether.[22d]

It should be noted that it was critical for us to access the natural product to assign absolute configurations for tertiary all-alkyl substituted boronic esters derived from substrates **37**. Few chiral phosphonates are known in the literature and few other straightforward alternate routes are available to assign absolute configurations of phosphonate-functionalized chiral tertiary boronic esters. Our initial plans towards the formal total synthesis of bakuchiol involved CAHB of the skipped diene substrate (*E*)-**37s** (Chapter 3), a successful CAHB of which, followed by vinylation of the formed β-boronate would have directly afforded intermediate **82** (Figure 4.3) in a much shorter and efficient synthetic sequence. However, the synthetic plan was not successful because the distal trisubstituted alkene in the substrate (*E*)-**37s** underwent competing reaction under the standard CAHB conditions. Therefore, we resorted to carrying out CAHB of substrate (*E*)-**37x** with a protected hydroxyl group that was eventually transformed into the terminal

trisubstituted alkene in the intermediate **82** in the successful sequence leading to (*S*)-(+)-bakuchiol methyl ether (Figure 4.6).

4.7. Summary and outlook

In this chapter, stereospecific transformations of three different classes of phosphonate-functionalized chiral boronic esters are documented: (i) tertiary benzylic boronic esters (*e.g.* **6a**), (ii) secondary benzylic boronic esters (*e.g.* **19a**), and (iii) all-alkyl substituted tertiary boronic esters (*e.g.* **37a**). Utility of these bifunctional molecules was further demonstrated by sequential transformation of the boronic ester and/or phosphonate functionalities in (i) phosphonate-unmasking via oxophosphonate intermediates (Figure 4.3), and (ii) construction of the skipped diene subunit in the formal total synthesis of bakuchiol using thiophosphonate olefination developed by Corey (Figure 4.6).[24]

While efficient stereospecific C-B bond transformations demonstrate the synthetic utility of these phosphonate-functionalized, chiral boronic esters, we also identified certain limitations with these functionalized systems. Stereospecific C-B bond transformations are typically developed for chiral boronic esters that are usually non-functionalized with hydrocarbon backbones or are minimally functionalized with inert functional groups such as ethers. Application of existing literature procedures on our functionalized chiral boronic esters frequently led to functional group tolerance issues. For instance, direct C-B to C-N bond substitution was never successful in our system mainly because the common methods employed to do so require very strong Lewis acids such as BCl_3 and $SiCl_4$ to transform the chiral boronic ester or the corresponding trifluoroborate salt to a more reactive dichloroborane intermediate.[4b,19] Phosphonates are not stable in the presence of such strong

Lewis acids and phosphonate-functionalized chiral tertiary boronic esters undergo decomposition and hydrolysis leading to a rather messy reaction mixture on attempted C-B to C-N transformations. However, direct C-B to C-N bond transformation was possible for chiral secondary boronic esters (*e.g.* **19a**) via the S_E2 reaction with the corresponding ate-complex.[3]

Acidity of the phosphonate α-H's (pKa ~ 30-35) presented problems while performing direct one-carbon homologations of phosphonate-functionalized chiral boronic esters using either dichloromethyl lithium or bromomethyl lithium, both of which are generated in-situ via reaction of the corresponding boronic ester with either dichloromethane or dibromomethane and butyllithium. Performing these reactions with phosphonates bearing α-H's resulted in deprotonation at the α-position leading to non-specific reactions and overall complicated reaction mixtures.

Aggarwal's vinylation/cross-coupling with electron rich 5-membered ring aromatics is among the most successful stereospecific C-B bond transformations carried out for these phosphonate-functionalized chiral boronic esters.[14,15] This is presumably because even though the initial addition of excess vinyl magnesium bromide or the aryl lithium results in deprotonation of the phosphonate α-position, the subsequent addition of the electrophile in an alcohol solvent results in rapid re-protonation of the phosphonate α-carbanion and capture of the electrophile by the boron-ate complex leading to stereospecific 1,2-B-to-C migration (*e.g.* synthesis of **56**, **57**, **67**, **68**, **73a** and **74a**).

Specific classes of phosphonate-functionalized chiral boronic esters presented unique challenges towards stereospecific functionalization. Trialkyl substituted chiral tertiary boronic esters had significant reactivity issues. For example, transformations such

as stereospecific protodeboronation and rhodium-catalyzed addition to aromatic aldehydes did not occur under standard conditions. On the other hand, several attempted stereospecific transformations with the phosphonate-functionalized chiral tertiary benzylic boronic esters resulted in high degrees of protodeboronation side products.

Phosphonate unmasking via hydroxy and oxophosphonate intermediates was carried out to afford a variety of common functionality appended to the quaternary chiral stereocenter (Figure 4.3). The chiral boronic ester **6a** was transformed to an ethyl group in **58** (via vinylation followed by reduction) prior to phosphonate α-oxidation. While the transformation of the boronic ester to an ethyl group was carried out because several of the final unmasked products (*e.g.* **60**, **62**, **64**, **65** and **66**) are known compounds previously reported in literature and this helped us reverify absolute configuration assigned to **6a**, however, in principle the boronic ester could be transformed into any functionality/group as long as the substituted functionality survives the conditions employed for α- oxidation.

In summary, the phosphonate-functionalized chiral boronic esters are highly versatile chiral synthons and can be further refunctionalized via stereospecific C-B bond transformations as well as via the chemistry of the phosphonate-functionality (thiophosphonate olefination and α- oxophosphonates). Diverse chiral phosphonates bearing a quaternary all-carbon stereocenter can be accessed and product utility in the context of total synthesis of a cytotoxic natural product further illustrates the potential of the chemistry. The chemistry developed as part of this dissertation should be of broad interest to chemists working in the field of asymmetric catalysis, chiral boron chemistry, chiral phosphonate chemistry and medicinal chemistry.

4.8. References

(1) (a) Sandford, C.; Aggarwal, V. K. "Stereospecific functionalizations and transformations of secondary and tertiary boronic esters" *Chem. Commun.*, **2017**, *53*, 5481; (b) Leonori, D.; Aggarwal, V. K. "Stereospecific Couplings of Secondary and Tertiary Boronic Esters" *Angew. Chem., Int. Ed.*, **2014**, *54*, 1082.

(2) C&EN Cover Story "Betting On Boron" March 11, 2011 (Volume 89, pp. 18-19) URL: https://pubs.acs.org/cen/coverstory/89/8912cover3.html

(3) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. "Ate Complexes of Secondary Boronic Esters as Chiral Organometallic-Type Nucleophiles for Asymmetric Synthesis" *J. Am. Chem. Soc.*, **2011**, *133*, 16794.

(4) For selected examples, see (a) Smith, S. M.; Hoang, G. L.; Pal, R.; Khaled, M. O. B.; Pelter, L. S. W.; Zeng, X. C.; Takacs, J. M. "γ-Selective directed catalytic asymmetric hydroborationof 1,1-disubstituted alkenes" *Chem. Commun.*, **2012**, *48*, 12180. (b) Hoang, G. L.; Yang, Z. D.; Smith, S. M.; Pal, R.; Miska, J. L.; Pérez, D. E.; Pelter, L. S. W.; Zeng, X. C.; Takacs, J. M. "Enantioselective Desymmetrization via Carbonyl-Directed Catalytic Asymmetric Hydroboration and Suzuki–Miyaura Cross-Coupling" *Org. Lett.*, **2015**, *17*, 940. (c) Shoba, V. M.; Thacker, N. C.; Bochat, A. J.; Takacs, J. M. "Synthesis of Chiral Tertiary Boronic Esters by Oxime-Directed Catalytic Asymmetric Hydroboration" *Angew. Chem., Int. Ed.*, **2016**, *55*, 1465. (d) Hoang, G. L.; Takacs, J. M. " Enantioselective γ-borylation of unsaturated amides and stereoretentive Suzuki–Miyaura cross-coupling" *Chem. Sci.*, **2017**, *8*, 4511. (e) Bochat, A. J.; Shoba, V. M.; Takacs, J. M. "Ligand-Controlled Regiodivergent Enantioselective Rhodium-Catalyzed Alkene Hydroboration" *Angew. Chem., Int. Ed.*, **2019**, *58*, 9434.

(5) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, W. L. "Intramolecular Regioselective Insertion into Unactivated Prochiral Carbon−Hydrogen Bonds with Diazoacetates of Primary Alcohols Catalyzed by Chiral Dirhodium(II) Carboxamidates. Highly Enantioselective Total Synthesis of Natural Lignan Lactones" *J. Org. Chem.*, **1996**, *61*, 9146.

(6) Dembitsky, V. M.; Al Quntar, A. A. A.; Srebnik, M. "Natural and Synthetic Small Boron-Containing Molecules as Potential Inhibitors of Bacterial and Fungal Quorum Sensing" *Chem. Rev.* **2011**, *111*, 209.

(7) Sharma, N.; Sharma, D. *J.* "An upcoming drug for onychomycosis: Tavaborole" *Pharmacol Pharmacother*, **2015**, *6*, 236.

(8) Horsman, G. P.; Zechel, D. L. "Phosphonate Biochemistry" *Chem. Rev.*, **2017**, *117*, 5704.

(9) (a) Kaplan, A. P.; Bartlett, P. A. "Synthesis and evaluation of an inhibitor of carboxypeptidase A with a Ki value in the femtomolar range" *Biochemistry* **1991**, *30*, 8165. (b) Tebby, J. C.; Kukhar, V. P., Hudson, H. R., Eds. "Aminophosphonic and aminophosphinic acids: chemistry and biological activity" John Wiley & Sons Ltd: Chichester, 2000.

(10) For a review of synthetic methods to construct α- and βaminophosphonates, see: Ma, J. A. " Catalytic asymmetric synthesis of α- and β-amino phosphonic acid derivatives" *Chem. Soc. Rev.* **2006**, *35*, 630.

(11) (a) Yan, Z.; Wu, B.; Gao, X.; Chen, M.-W.; Zhou, Y.-G. "Enantioselective Synthesis of α-Amino Phosphonates via Pd-Catalyzed Asymmetric Hydrogenation" *Org. Lett.*, **2016**, *18*, 692. (b) Corbett, M. T.; Johnson, J. S. " Diametric Stereocontrol in Dynamic Catalytic

Reduction of Racemic Acyl Phosphonates: Divergence from α-Keto Ester Congeners" *J. Am. Chem. Soc.* **2013**, *135*, 594. (c) Zhang, J.; Li, Y.; Wang, Z.; Ding, K. " Asymmetric hydrogenation of α- and β-enamido phosphonates: rhodium(I)/monodentate phosphoramidite catalyst" *Angew. Chem., Int. Ed.,* **2011**, *50*, 11743.

(12) Chakrabarty, S.; Takacs, J. M. "Phosphonate-Directed Catalytic Asymmetric Hydroboration: Delivery of Boron to the More Substituted Carbon, Leading to Chiral Tertiary Benzylic Boronic Esters" *ACS Catal.,* **2018**, *8*, 10530.

(13) Nave, D.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. "Protodeboronation of Tertiary Boronic Esters: Asymmetric Synthesis of Tertiary Alkyl Stereogenic Centers" *J. Am. Chem. Soc.,* **2010**, *132*, 17096.

(14) Rasappan, R.; Aggarwal, V. K. " Synthesis of hydroxyphthioceranic acid using a traceless lithiation–borylation–protodeboronation strategy" *Nat. Chem.,* **2014**, *6*, 810.

(15) Bagutski, V.; Ros, A.; Aggarwal, V. K. "Improved method for the conversion of pinacolboronic esters into trifluoroborate salts: facile synthesis of chiral secondary and tertiary trifluoroborates" *Tetrahedron* **2009**, 65, 9956.

(16) For selected examples of metal-catalyzed cross-coupling of chiral secondary trifluorborate salts, see: (a) Li, L.; Zhao, S.; JoshiPangu, A.; Diane, M.; Biscoe, M. R. "Stereospecific Pd-Catalyzed Cross-Coupling Reactions of Secondary Alkylboron Nucleophiles and Aryl Chlorides" *J. Am. Chem. Soc.,* **2014**, *136*, 14027. (b) Feng, X.; Jeon, H.; Yun, J. "Regio- and enantioselective copper(I)-catalyzed hydroboration of borylalkenes: asymmetric synthesis of 1,1-diborylalkanes" *Angew. Chem., Int. Ed.,* **2013**, *52*, 3989. (c) Lee, J. C. H.; McDonald, R.; Hall, D. G. "Enantioselective preparation and chemoselective cross-coupling of 1,1-diboron compounds" *Nat. Chem.,* **2011**, *3*, 894.

(17) Primer, D. N.; Molander, G. A. "Enabling the CrossCoupling of Tertiary Organoboron Nucleophiles through RadicalMediated Alkyl Transfer" *J. Am. Chem. Soc.* **2017**, *139*, 9847.

(18) Harris, M. R.; Li, Q.; Lian, Y.; Xiao, J.; Londregan, A. T. "Construction of 1-Heteroaryl-3-azabicyclo[3.1.0]hexanes by sp^3–sp^2 Suzuki−Miyaura and Chan−Evans−Lam Coupling Reactions of Tertiary Trifluoroborates" *Org. Lett.*, **2017**, *19*, 2450.

(19) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. "Rhodium Catalyzed Asymmetric 1,4-Addition to 1-Alkenylphosphonates" *J. Am. Chem. Soc.*, **1999**, *121*, 11591.

(20) For medicinal relevance of chiral quaternary carbons bearing two aryl groups, see: (a) Loach, R. P.; Fenton, O. S.; Movassaghi, M. "Concise Total Synthesis of (+)-Asperazine, (+)-Pestalazine A, and (+)-iso-Pestalazine A. Structure. Revision of (+)-Pestalazine A" *J. Am. Chem. Soc.*, **2016**, *138*, 1057. (b) Trost, B. M.; Xie, J.; Sieber, J. D. "The Palladium Catalyzed Asymmetric Addition of Oxindoles and Allenes: An Atom-Economical Versatile Method for the Construction of Chiral Indole Alkaloids" *J. Am. Chem. Soc.*, **2011**, *133*, 20611.

(21) Jang, K. P.; Hutson, G. E.; Johnston, R. C.; McCusker, E. O.; Cheong, P. H. Y.; Scheidt, K. A. "Asymmetric Homoenolate Additions to Acyl Phosphonates through Rational Design of a Tailored N-Heterocyclic Carbene Catalyst" *J. Am. Chem. Soc.*, **2014**, *136*, 76.

(22) Pogatchnik, D. M.; Wiemer, D. F. "Enantioselective Synthesis of α-Hydroxy Phosphonates via Oxidation with (Camphorsulfonyl)-oxaziridines" *Tetrahedron Lett.*, **1997**, *38*, 3495.

(23) Williamson, K. S.; Michaelis, D. J.; Yoon, T. P. "Advances in the Chemistry of Oxaziridines" *Chem. Rev.* **2014**, *114*, 8016.

(24) Rowe, B. J.; Spilling, C. D. "Stereospecific Pd(0)-Catalyzed Arylation of an Allylic Hydroxy Phosphonate Derivative: Formal Synthesis of (S)-(+)-ar-Turmerone" *J. Org. Chem.*, **2003**, *68*, 9502.

(25) Potter, B.; Edelstein, E. K.; Morken, J. P. "Modular, Catalytic Enantioselective Construction of Quaternary Carbon Stereocenters by Sequential Cross-Coupling Reactions" *Org. Lett.* **2016**, *18*, 3286.

(26) (a) Jang, K. P.; Hutson, G. E.; Johnston, R. C.; McCusker, E. O.; Cheong, P. H. Y.; Scheidt, K. A. "Asymmetric Homoenolate Additions to Acyl Phosphonates through Rational Design of a Tailored NHeterocyclic Carbene Catalyst" *J. Am. Chem. Soc.*, **2014**, *136*, 76; (b) Corbett, M. T.; Johnson, J. S. "Diametric Stereocontrol in Dynamic Catalytic Reduction of Racemic Acyl Phosphonates: Divergence from α-Keto Ester Congeners" *J. Am. Chem. Soc.*, **2013**, *135*, 594.

(27) Gao, M.; Wang, D. X.; Zheng, Q. Y.; Huang, Z. T.; Wang, M. X. "Remarkable Electronic and Steric Effects in the Nitrile Biotransformations for the Preparation of Enantiopure Functionalized Carboxylic Acids and Amides: Implication for an Unsaturated Carbon−Carbon Bond Binding Domain of the Amidase" *J. Org. Chem.*, **2007**, *72*, 6060.

(28) Yu, K.; Lu, P.; Jackson, J. J.; Nguyen, T. A. D.; Alvarado, J.; Stivala, C. E.; Ma, Y.; Mack, K. A.; Hayton, T. W.; Collum, D. B.; Zakarian, A. "Lithium Enolates in the Enantioselective Construction of Tetrasubstituted Carbon Centers with Chiral Lithium Amides as Noncovalent Stereodirecting Auxiliaries" *J. Am. Chem. Soc.*, **2017**, *139*, 527.

(29) For substitution reactions involving oxophosphonates, see: (a) Liu, Y.; Liu, X.; Hu, H.; Guo, J.; Xia, Y.; Lin, L.; Feng, X. "Synergistic Kinetic Resolution and Asymmetric Propargyl Claisen Rearrangement for the Synthesis of Chiral Allenes" *Angew. Chem., Int. Ed.*, **2016**, *55*, 4054. (b) Tan, J.; Cheon, C. H.; Yamamoto, H. "Catalytic Asymmetric Claisen Rearrangement of Enolphosphonates: Construction of Vicinal Tertiary and All-Carbon Quaternary Centers" *Angew. Chem., Int. Ed.* **2012**, *51*, 8264.

(30) Evans, P. A.; Oliver, S.; Chae, J. "Rhodium-Catalyzed Allylic Substitution with an Acyl Anion Equivalent: Stereospecific Construction of Acyclic Quaternary Carbon Stereogenic Centers" *J. Am. Chem. Soc.*, **2012**, *134*, 19314.

(31) Maeda, H.; Takahashi, K.; Ohmori, H. "Reactions of acyl tributylphosphonium chlorides and dialkyl acylphosphonates with Grignard and organolithium reagents" *Tetrahedron* **1998**, *54*, 12233.

(32) Chakrabarty, S.; Palencia, H.; Morton, M. D.; Carr, R. O.; Takacs, J. M. "Facile access to functionalized chiral secondary benzylic boronic esters via catalytic asymmetric hydroboration" *Chem. Sci.*, **2019**, *10*, 4854.

(33) For examples of stereoretentive cross-coupling of chiral secondary organoboron derivatives, see ref. 4b, 4d and (a) Blaisdell, T. P; Morken, J. P. " Hydroxyl-Directed Cross-Coupling: A Scalable Synthesis of Debromohamigeran E and Other Targets of Interest" *J. Am. Chem. Soc.*, **2015**, *137*, 8712; (b) Daini, M.; Suginome, M. "Palladium-Catalyzed, Stereoselective, Cyclizative Alkenylboration of Carbon−Carbon Double Bonds through Activation of a Boron−Chlorine Bond" *J. Am. Chem. Soc.*, **2011**, *133*, 4758.

(34) For examples of stereoinvertive cross-coupling of chiral secondary organoboron derivatives, see: (a) Lee, J. C. H.; Sun, H.-Y.; Hall, D. G. " Optimization of Reaction and

Substrate Activation in the Stereoselective Cross-Coupling of Chiral 3,3-Diboronyl Amides" *J. Org. Chem.*, **2015**, *80*, 7134; (b) Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. " Stereospecific Pd-Catalyzed Cross-Coupling Reactions of Secondary Alkylboron Nucleophiles and Aryl Chlorides" *J. Am. Chem. Soc.*, **2014**, *136*, 14027; (c) Lee, J. C.; McDonald, R.; Hall, D. G. " Enantioselective preparation and chemoselective cross-coupling of 1,1-diboron compounds" *Nat. Chem.*, **2011**, *3*, 894; (d) Awano, T.; Ohmura, T.; Suginome, M. " Inversion or Retention? Effects of Acidic Additives on the Stereochemical Course in Enantiospecific Suzuki–Miyaura Coupling of α-(Acetylamino)benzylboronic Esters" *J. Am. Chem. Soc.*, **2011**, *133*, 20738; (e) Sandrock, D. L.; Jean-Gerard, L.; Chen, C.; Dreher, S. D.; Molander, G. A. " Stereospecific Cross-Coupling of Secondary Alkyl β-Trifluoroboratoamides" *J. Am. Chem. Soc.*, **2010**, *132*, 17108; (f) Ohmura, T.; Awano, T.; Suginome, M. "Stereospecific Suzuki−Miyaura Coupling of Chiral α-(Acylamino)benzylboronic Esters with Inversion of Configuration" *J. Am. Chem. Soc.*, **2010**, *132*, 13191.

(35) For ligand-controlled stereoretentive and stereoinvertive cross-coupling of chiral secondary organoboron derivatives, see: Zhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. R. " Enantiodivergent Pd-catalyzed C–C bond formation enabled through ligand parameterization" *Science* **2018**, *362*, 670.

(36) For a perspective on enantiospecific and iterative Suzuki-Miyaura cross-couplings, see: Rygus, J. P. G.; Crudden, C. M. " Enantiospecific and Iterative Suzuki–Miyaura Cross-Couplings" *J. Am. Chem. Soc.*, **2017**, *139*, 18124.

(37) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. "Cross Coupling Reactions of Chiral Secondary Organoboronic Esters With Retention of Configuration" *J. Am. Chem. Soc.,* **2009**, *131*, 5024.

(38) Ros, A.; Aggarwal, V. K. " Complete Stereoretention in the Rhodium-Catalyzed 1,2-Addition of Chiral Secondary and Tertiary Alkyl Potassium Trifluoroborate Salts to Aldehydes" *Angew. Chem., Int. Ed.,* **2009**, *48*, 6289.

(39) Hu, N.; Zhao, G.; Zhang, Y.; Liu, X.; Li, G.; Tang, W. "Synthesis of Chiral α-Amino Tertiary Boronic Esters by Enantioselective Hydroboration of α-Arylenamides" *J. Am. Chem. Soc.,* **2015**, *137*, 6746.

(40) Chakrabarty, S.; Takacs, J. M. "Synthesis of Chiral Tertiary Boronic Esters: Phosphonate-Directed Catalytic Asymmetric Hydroboration of Trisubstituted Alkenes", *J. Am. Chem. Soc.,* **2017**, *139*, 6066.

(41) Bueschleb, M.; Dorich, S.; Hanessian, S.; Tao, D.; Schenthal, K. B.; Overman, L. E. "Synthetic Strategies toward Natural Products Containing Contiguous Stereogenic Quaternary Carbon Atoms" *Angew. Chem., Int. Ed.,* **2016**, *55*, 4156 and references cited therein.

(42) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. " Enantiospecific sp(2)-sp(3) coupling of secondary and tertiary boronic esters" *Nat. Chem.* **2014**, *6*, 584.

(43) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; LaroucheGauthier, R.; Scott, H. K.; Aggarwal, V. K. " Enantioselective Construction of Quaternary Stereogenic Centers from Tertiary Boronic Esters: Methodology and Applications" *Angew. Chem., Int. Ed.* **2011**, *50*, 3760.

(44) Hon, Y.-S.; Lin, S. W.; Lu, L.; Chen, Y.-J. " The mechanistic study and synthetic applications of the base treatment in the ozonolytic reactions" *Tetrahedron* **1995**, *51*, 5019.

(45) Chatterjee, B.; Gunanathan, C. "Ruthenium catalyzed selective hydrosilylation of aldehydes" *Chem. Commun.*, **2014**, *50*, 888.

(46) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. " Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures" *J. Org. Chem.*, **1996**, *61*, 3849.

(47) (a) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. " Direct Stereospecific Amination of Alkyl and Aryl Pinacol Boronates" *J. Am. Chem. Soc.* **2012**, *134*, 16449. (b) Bagutski, V.; Elford, T. G.; Aggarwal, V. K. " Synthesis of Highly Enantioenriched C-Tertiary Amines From Boronic Esters: Application to the Synthesis of Igmesine" *Angew. Chem., Int. Ed.*, **2011**, *50*, 1080.

(48) Zhang, L.; Zuo, Z.; Wan, Z.; Huang, Z. "Cobalt-Catalyzed Enantioselective Hydroboration of 1,1-Disubstituted Aryl Alkenes" *J. Am. Chem. Soc.*, **2014**, *136*, 15501.

(49) (a) Patel, H. H.; Sigman, M. S. "Enantioselective Palladium-Catalyzed Alkenylation of Trisubstituted Alkenols To Form Allylic Quaternary Centers" *J. Am. Chem. Soc.*, **2016**, *138*, 14226. For synthesis of α-amino phosphonates via Curtis rearrangement, see: (b) Moore, J. D.; Sprott, K. T.; Hanson, P. R. "Conformationally Constrained α-Boc-Aminophosphonates via Transition Metal-Catalyzed/Curtius Rearrangement Strategies" *J. Org. Chem.*, **2002**, *67*, 8123.

(50) (a) Majeed, R.; Reddy, M. V.; Chinthakindi, P. K.; Sangwan, P. L.; Hamid, A.; Chashoo, G.; Saxena, A. K.; Koul, S. " Bakuchiol derivatives as novel and potent cytotoxic

agents: A report" *Eur. J. Med. Chem.*, **2012**, *49*, 55. For recent syntheses of bakuchiol, see: (b) Xiong, Y.; Zhang, G. " Enantioselective Synthesis of Quaternary Stereocenters via Chromium Catalysis" *Org. Lett.*, **2016**, *18*, 5094. (c) Esumi, T.; Yamamoto, C.; Fukuyama, Y. " A Short Synthesis of (+)-Bakuchiol" *Synlett* **2013**, *24*, 1845. (d) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. "Synthesis of Quaternary Carbon Stereogenic Centers through Enantioselective Cu-Catalyzed Allylic Substitutions with Vinylaluminum Reagents" *J. Am. Chem. Soc.* **2010**, *132*, 14315.

(51) Parikh, J. R.; Doering, W. v. E. "Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide" *J. Am. Chem. Soc.*, **1967**, *89*, 5505.

(52) Reichwein, J. F.; Pagenkopf, B. L. "A New Horner−Wadsworth−Emmons Type Coupling Reaction between Nonstabilized β-Hydroxy Phosphonates and Aldehydes or Ketones" *J. Am. Chem. Soc.*, **2003**, *125*, 1821.

(53) Corey, E. J.; Kwiatkowski, G. T. " The Synthesis of Olefins from O,O'-Dialkyl β-Lithioalkylphosphonothioate Esters" *J. Am. Chem. Soc.*, **1966**, *88*, 5654.

(54) Yamagishi, T.; Muronoi, S.; Hikishima, S.; Shimeno, H.; Soeda, S.; Yokomatsu, T. "Diastereoselective Synthesis of γ-Amino-δ-hydroxy-α,α-difluorophosphonates: A Vehicle for Structure−activity Relationship Studies on SMA-7, a Potent Sphingomyelinase Inhibitor" *J. Org. Chem.*, **2009**, *74*, 6350 and references cited therein.

(55) The stereochemistry of CAHB of all-alkyl trisubstituted alkenes (**37**) is assigned based on correlation via this synthesis.

CHAPTER FIVE: EXPERIMENTAL DETAILS AND CHARACTERIZATION DATA

5.1. General Information

All reactions were carried out under a dry nitrogen atmosphere unless otherwise indicated. Tetrahydrofuran (THF) was freshly distilled over sodium and benzophenone prior usage in CAHB reactions. Pinacolborane (pinBH) was obtained from Acros Organics MS (97% purity, stabilized with triethylamine) and was distilled under nitrogen (760 mm Hg, 150 ^{o}C) prior to use. For long term storage, the distilled pinacolborane was stored in freezer in 8 mL vials with airtight screw cap under nitrogen. All substrates were subjected to high vacuum (*ca.* 1 mm Hg) at 100 ^{o}C for an hour to remove any residual diethyl phosphite, triethyl phosphite or triethyl phosphate. The latter are trace contaminants in commercial diethyl phosphite, and if present in even trace quantitates in the substrate, can greatly diminish the activity of the chiral rhodium catalyst. For convenience, CAHB reactions were set up in glovebox under a dry nitrogen atmosphere. Yields reported for the boronic esters/derivatives are an average of at least 2 runs.

Synthesized compounds are purified by flash chromatography using EMD Silica Gel 60 Geduran®. Thin Layer Chromatography analyses are performed on Analtech Silica Gel HLF (0.25 mm) precoated analytical plates and visualized with the use of either a handheld short wavelength UV light, iodine stain (molecular iodine adsorbed on silica gel) or $KMnO_4$ stain ($KMnO_4$, K_2CO_3, NaOH and H_2O). Chiral HPLC analyses were performed with the use of either (1) An ISCO model 2360 HPLC and Chiral Technologies Inc: monitored with US-VIS detector (Shimadzu SPD-10AVP/10AVP; or (2) A 1220 Infinity II LC (Agilent Technologies) Model Number G4290C. Typical λ used for HPLC UV detectors = 210 nm unless otherwise indicated. Daicel HPLC 250 x 4.6 mm columns are

used for chiral separations (specific column used is indicated in the appropriate experimental section). OpenLAB CDS ChemStation Edition (Rev. C.01.08(210)) software is used for integration/analysis of HPLC results.

NMR spectra were recorded on 300, 400 or 700 MHz Bruker Advance NMR spectrometers in the deuterated solvent specified. The solvent residual peaks were used for reference and spectra calibration unless otherwise indicated. Rather complex splitting patterns are found in the NMR spectra due to phosphorus-hydrogen coupling ($J_{P\text{-}H}$) and phosphorus-carbon coupling ($J_{C\text{-}P}$). Phosphorus-carbon coupling is seen up to 5 bonds ($^{5}J_{C\text{-}P}$); these splitting patterns were resolved, and the corresponding coupling constants assigned. The quaternary carbon atoms connected directly to boron in tertiary boronic esters or trifluoroborate salts were not seen in the ^{13}C NMR spectra due to quadrupolar relaxation of boron. Peaks in the NMR spectra are described as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), quin (quintet), dd (doublet of doublets), m (unresolved multiplet), etc. In several cases, C_6D_6 proved to be a superior NMR solvent for resolving the signals for diastereomers in ^{31}P NMR spectra for diastereoenriched chiral boronic esters. However, ^{1}H and ^{13}C NMR data are reported only for the major diastereomer in this dissertation.

IR spectra were recorded using an Avatar 360 FT-IR instrument as neat films. Optical rotations were typically measured as 1.0 g/100 mL (*i.e.*, c = 1.0) solutions in the indicated solvent (usually in $CHCl_3$ used directly from commercial bottles) using an Autopol III automatic polarimeter. Specific rotation values are reported in units of deg dm^{-1} cm^3 g^{-1}. EI/ESI-HRMS analyses were carried out by the Nebraska Center for Mass Spectrometry.

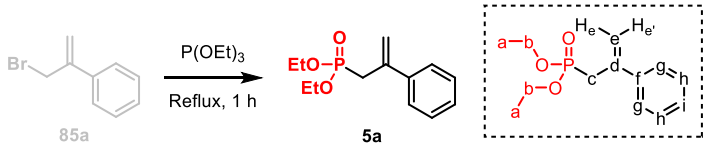
The Routine Preparation of Synthetic Precursors. The Supporting Information given below for the preparation and CAHB of allylic phosphonates starts with the allyl bromide. These precursors were obtained either from (1) direct allylic bromination of α-methyl styrene using NBS (for substrate **5a**),[1] or (2) bromination of allylic alcohols using PBr_3[2] or NBS/PPh_3.[3] The allyl alcohols were obtained either via the CuI-catalyzed addition of the corresponding aryl Grignard reagent to propargyl alcohol[4] or via Suzuki cross-coupling of the arylboronic acids with 2-iodoprop-2-en-1-ol (e.g., for thiophene derivatives **5l** and **5m**; Typical Suzuki cross-coupling conditions: 5 mol% $Pd(PPh_3)_4$, 2 eq. Cs_2CO_3, EtOH at 70ºC for 12 hours), or via the Horner-Wadsworth-Emmons olefination with the appropriate aldehyde. The allyl alcohol precursors for the β-aryl trisubstituted substrates were derived from (1) Suzuki cross-coupling reaction of the corresponding (*Z*)-β-iodo-γ-(alkyl/aryl)-2-en-1-ol with the arylboronic acid derivatives (Typical conditions: 5 mol% $Pd(PPh_3)_4$, 1.5 equiv. boronic acid, 2 eq. Cs_2CO_3, EtOH reflux for 12-24 hours) for substrates in which the phosphonate and the γ-alkyl chain are trans to each other; (2) Stille cross coupling of the corresponding (*E*)-β-tributylstannyl-γ-(alkyl)-2-en-1-ol (with corresponding aryl bromides; typical conditions: 5 mol% $Pd(PPh_3)_4$, 1.5 equiv. aryl bromide, 2 eq. Cs_2CO_3, EtOH reflux for 12-24 hours) for substrates in which the phosphonate and the γ-alkyl chain are cis to each other. The vinyl (alkenyl) tin precursors were obtained via Pd-catalyzed hydrostannation of the corresponding alkynyl esters.[5] The α-vinyl tin allyl esters were reduced to the corresponding alcohols using DIBAL-H prior to their use in Stille cross coupling. Davis' Oxaziridine was prepared according to reported protocols.[6]

Comment on the Oxidation. We found that attempted oxidation of the crude CAHB reaction mixture led to unexpected side products and lower yields of the alcohol. In some cases, the boronic esters could not be cleanly separated by flash chromatography; nonetheless, the partially purified mixture of boronic esters and reduced products (if any) could be efficiently oxidized using standard conditions.

Comment on Absolute Configuration. The presence of the 2-thiophene subunit in the beta position of the substrates requires that the typical *E*-substrate substitution pattern is correctly described as Z since the 2-thienyl unit is assigned the highest priority. This also results in a switch from the expected *R*-configuration of boronic esters obtained using (*R*,*R*)-**T2** to *S* for the 2-thienyl products.

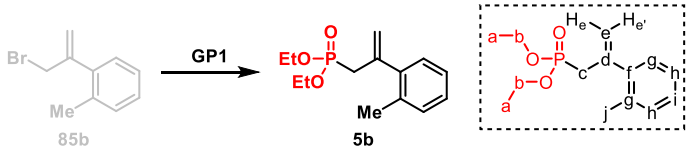
5.2. Synthesis of substrates

Synthesis of methylidene substrates

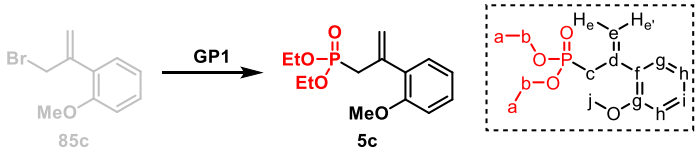


General procedure for the synthesis of conjugated allyl methylidene phosphonates via Michaelis-Arbuzov Rearrangement (GP1). Synthesis of **5a**: A mixture of allyl bromide **85a** (1.00 g, 5.07 mmol, 1.00 eq) and triethyl phosphite (0.38 mL, 2.20 mmol, 1.10 eq) is heated to reflux for 1 hour. Afterwards, the reaction mixture is cooled down to room temperature and flash chromatography on silica gel (ethyl acetate/hexanes 2:1) affords the desired phosphonate substrate **5a** (1.13 g, 88%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.26 (5H, m, aryl), 5.53 (1H, dd, *J* = 5.5 ($^4J_{P\text{-}H}$), 0.8 ($^4J_{H\text{-}H}$) Hz, H_e or $H_{e'}$), 5.37 (1H, dd, *J* = 5.5 ($^4J_{P\text{-}H}$), 0.8

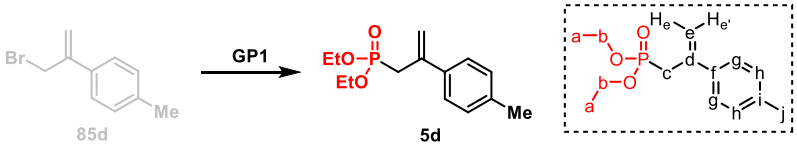
($^4J_{H\text{-}H}$) Hz, H_e or $H_{e'}$), 4.09-3.94 (4H, m, b), 3.08 (2H, dd, J = 22.4 ($^2J_{P\text{-}H}$), 0.8 ($^4J_{H\text{-}H}$) Hz, c), 1.21 (6H, t, J = 7.2 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.87 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, d), 138.89 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 128.44 (aryl), 127.88 (aryl), 126.45 (aryl), 117.33 (d, $^3J_{C\text{-}P}$ = 11 Hz, e), 62.14 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b), 33.18 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 16.44 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.53 ppm; IR (neat) 2981 (aromatic C-H), 2906 (aliphatic C-H), 1624 (C=C), 1250 (P=O), 1052 (C-O), 1020 (C-O), 934 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{13}H_{19}O_3P$ = 254.1072, found 254.1071 *m/z*.



Synthesis of phosphonate functionalized alkene 5b: Following **GP1**, allyl bromide **85b** (528 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5b** (590 mg, 88%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.13 (4H, m, aryl), 5.50 (1H, d, J = 5.2 ($^4J_{P\text{-}H}$), 1.0 ($^4J_{H\text{-}H}$) Hz, H_e or $H_{e'}$), 5.13 (1H, d, J = 5.0 ($^4J_{P\text{-}H}$), 1.2 ($^4J_{H\text{-}H}$) Hz, H_e or $H_{e'}$), 4.05-3.88 (4H, m, b), 2.95 (2H, dd, J = 22 ($^2J_{P\text{-}H}$), 1.0 ($^4J_{H\text{-}H}$) Hz, c), 2.35 (3H, s, j), 1.20 (6H, t, J = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.15 (d, $^2J_{C\text{-}P}$ = 5 Hz, d), 139.73 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 134.98 (g), 130.34 (aryl), 128.76 (aryl), 127.41 (aryl), 125.64 (aryl), 119.59 (d, $^3J_{C\text{-}P}$ = 11 Hz, e), 61.87 (d, $^2J_{C\text{-}P}$ = 7 Hz, b), 35.01 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 20.09 (j), 16.40 (d, $^3J_{C\text{-}P}$ = 7 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.25 ppm; IR (neat) 2980 (aromatic C-H), 2906 (aliphatic C-H), 1633 (C=C), 1251 (P=O), 1052 (C-O), 1022 (C-O), 958 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{14}H_{21}O_3P$ = 268.1228, found 268.1226 *m/z*.

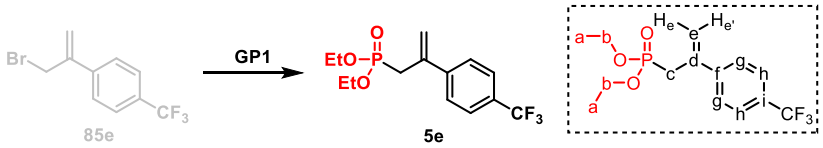


Synthesis of phosphonate functionalized alkene 5c: Following **GP1**, allyl bromide **85c** (568 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5c** (570 mg, 80%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.30 (2H, m, aryl), 6.95-6.87 (1H, m, aryl), 6.86 (1H, d, *J* = 8.0 Hz, h), 5.38-5.36 (1H, m, H_e or $H_{e'}$), 5.25 (1H, dd, *J* = 5.0 ($^4J_{P\text{-}H}$), 1.6 ($^4J_{H\text{-}H}$) Hz, H_e or $H_{e'}$), 3.99-3.87 (4H, m, b), 3.84 (3H, s, j), 3.18 (2H, dd, *J* = 21.6 ($^2J_{P\text{-}H}$), 1.0 ($^4J_{H\text{-}H}$) Hz, c), 1.70 (6H, t, *J* = 7.2 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.53 (g), 139.39 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 131.15 (d, $^2J_{C\text{-}P}$ = 4 Hz, d), 130.75 (aryl), 129.11 (aryl), 120.79 (aryl), 119.45 (d, $^3J_{C\text{-}P}$ = 12 Hz, e), 110.57 (h), 61.73 (d, $^2J_{C\text{-}P}$ = 6 Hz, b), 55.53 (j), 33.48 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 16.40 (d, $^3J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.34 ppm; IR (neat) 2980 (aromatic C-H), 2905 (aliphatic C-H), 1629 (C=C), 1598 (C=C), 1241 (P=O), 1047 (C-O), 1021 (C-O), 957 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{14}H_{21}O_4P$ = 284.1177, found 284.1167 *m/z*.

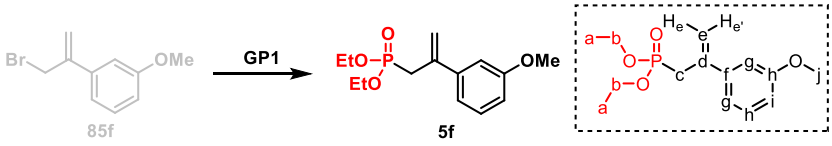


Synthesis of phosphonate functionalized alkene 5d: Following **GP1**, allyl bromide **85d** (528 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5d** (610 mg, 91%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, d, *J* = 8.0 Hz, g or h), 7.16 (2H, d, *J* = 8.0 Hz, g or h), 5.52 (1H, d, $^4J_{P\text{-}H}$ = 5.2 Hz, H_e or $H_{e'}$), 5.33 (1H, d, $^4J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 4.10-3.95 (4H, m, b), 3.07 (2H, d, $^2J_{P\text{-}H}$ = 22.4 Hz, c), 2.36 (3H, s, j), 1.23 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz,

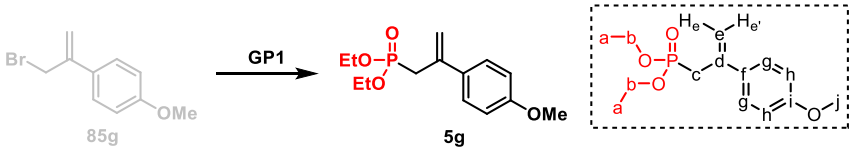
$CDCl_3$) δ 138.65 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 137.97 (d, $^2J_{C\text{-}P}$ = 5 Hz, d), 137.74 (i), 129.16 (g or h), 126.34 (g or h), 116.53 (d, $^3J_{C\text{-}P}$ = 10 Hz, e), 62.20 (d, $^2J_{C\text{-}P}$ = 7 Hz, b), 33.18 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 21.29 (j), 16.50 (d, $^3J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.72 ppm; IR (neat) 2980 (aromatic C-H), 2905 (aliphatic C-H), 1621 (C=C), 1514 (aromatic C=C), 1391 (aromatic C=C), 1249 (P=O), 1052 (C-O), 1021 (C-O), 939 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{14}H_{21}O_3P$ = 268.1228, found 268.1230 *m/z*.



Synthesis of phosphonate functionalized alkene 5e: Following **GP1**, allyl bromide **85e** (663 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5e** (580 mg, 72%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (4H, s, aryl), 5.59 (1H, d, $^4J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 5.45 (1H, d, $^4J_{P\text{-}H}$ = 5.2 Hz, H_e or $H_{e'}$), 4.10-3.96 (4H, m, b), 3.07 (2H, d, $^2J_{P\text{-}H}$ = 22 Hz, c), 1.22 (6H, t, *J* = 7.2 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.41 (d), 138.09 (d, $^3J_{C\text{-}P}$ = 11 Hz, f), 129.89 (q, $^2J_{C\text{-}F}$ = 32 Hz, i), 126.86 (j), 125.42 (q, $^3J_{C\text{-}F}$ = 4 Hz, h), 124.31 (q, $^1J_{C\text{-}F}$ = 271 Hz, CF_3), 119.27 (d, $^3J_{C\text{-}P}$ = 11 Hz, e), 62.26 (d, $^2J_{C\text{-}P}$ = 6 Hz, b), 33.21 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 16.45 (d, $^3J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.83 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.61 ppm; IR (neat) 2984 (aromatic C-H), 2907 (aliphatic C-H), 1616 (C=C), 1324 (C-F), 1250 (P=O), 1052 (C-O), 1023 (C-O), 959 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{14}H_{18}F_3O_3P$ = 322.0946, found 322.0950 *m/z*.

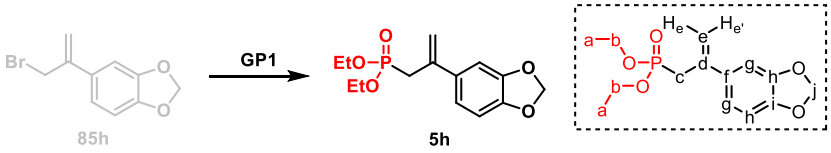


Synthesis of phosphonate functionalized alkene 5f: Following **GP1**, allyl bromide **85f** (568 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5f** (604 mg, 85%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, t, *J* = 8.0 Hz, aryl), 7.07-7.03 (2H, m, aryl), 6.83 (1H, dd, *J* = 2.0, 0.6 Hz, aryl), 5.52 (1H, d, $^{4}J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 5.36 (1H, d, $^{4}J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 4.09-3.94 (4H, m, b), 3.82 (3H, s, j), 3.05 (2H, d, $^{2}J_{P\text{-}H}$ = 22.0 Hz, c), 1.24 (6H, t, *J* = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.69 (h), 142.43 (d, $^{2}J_{C\text{-}P}$ = 4 Hz, d), 138.77 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, f), 129.39 (aryl), 118.96 (aryl), 117.47 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, e), 113.30 (aryl), 112.29 (aryl), 62.14 (d, $^{2}J_{C\text{-}P}$ = 6 Hz, b), 55.39 (j), 33.19 (d, $^{1}J_{C\text{-}P}$ = 138 Hz, c), 16.44 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.50 ppm; IR (neat) 3056 (aromatic C-H), 2980 (aliphatic C-H), 1687 (C=C), 1665 (C=C), 1249 (P=O), 1022 (C-O), 952 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{14}H_{21}O_4P$ = 284.1177, found 284.1175 *m/z*.

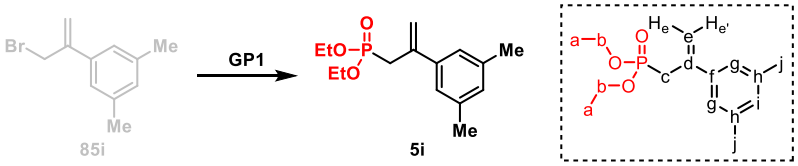


Synthesis of phosphonate functionalized alkene 5g: Following **GP1**, allyl bromide **85g** (568 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5g** (533 mg, 75%) as a colorless viscous oil: TLC analysis (ethyl acetate) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.8 Hz, g), 6.87 (2H, d, *J* = 8.8 Hz, g), 5.45 (1H, dd, *J* = 6.4 ($^{4}J_{P\text{-}H}$), 0.8 ($^{4}J_{H\text{-}H}$) Hz, H_e or $H_{e'}$), 5.26 (1H, d, $^{4}J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 4.09-3.94 (4H, m, b), 3.81 (3H, s, j), 3.04 (2H, d, $^{2}J_{P\text{-}H}$ = 22.0 Hz, c), 1.22 (6H, t, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.46 (h), 138.11 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, f), 133.23 (d, $^{2}J_{C\text{-}P}$ = 4 Hz, d), 127.59 (g), 115.64 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, e), 113.75 (h), 62.14 (d, $^{2}J_{C\text{-}P}$ = 6 Hz, b), 55.43 (j), 33.25 (d, $^{1}J_{C\text{-}P}$ = 137 Hz, c), 16.47 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.72 ppm; IR (neat)

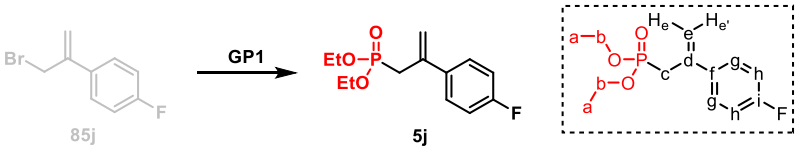
3056 (aromatic C-H), 2980 (aliphatic C-H), 1606 (C=C), 1512 (aromatic C=C), 1246 (P=O), 1051 (C-O), 1021 (C-O), 958 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{14}H_{21}O_4P$ = 284.1177, found 284.1171 *m/z*.



Synthesis of phosphonate functionalized alkene 5h: Following **GP1**, allyl bromide **85h** (602 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5h** (537 mg, 72%) as a colorless oil (Note: This substrate is air sensitive and slowly decomposes on exposure to air and turns into a dark brown mass. This compound was stored in vial with airtight screw cap under nitrogen in the freezer): TLC analysis (ethyl acetate) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (1H, d, *J* = 2.4 Hz, aryl), 6.97 (1H, d, *J* = 1.6 Hz, aryl), 6.78 (1H, d, *J* = 8.0 Hz, aryl), 5.96 (2H, s, j), 5.43 (1H, d, $^4J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 5.27 (1H, d, $^4J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 4.11-3.97 (4H, m, b), 3.01 (2H, d, $^2J_{P\text{-}H}$ = 22.4 Hz, c), 1.25 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.85 (h or i), 147.42 (h or i), 138.34 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 135.18 (d, $^2J_{C\text{-}P}$ = 4 Hz, d), 120.20 (aryl), 116.28 (d, $^3J_{C\text{-}P}$ = 11 Hz, e), 108.11 (aryl), 107.04 (aryl), 101.28 (j), 62.19 (d, $^2J_{C\text{-}P}$ = 7 Hz, b), 33.43 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 16.51 (d, $^3J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.52 ppm; IR (neat) 2980 (aromatic C-H), 2903 (aliphatic C-H), 1604 (C=C), 1489 (aromatic C=C), 1441 (aromatic C=C), 1231 (P=O), 1020 (C-O), 933 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{14}H_{19}O_5P$ = 298.0970, found 298.0974 *m/z*.

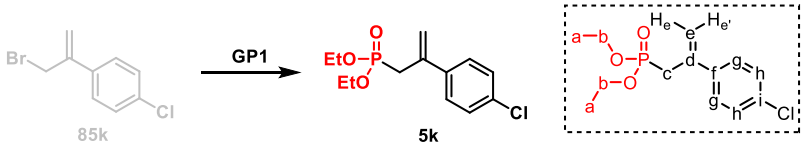


Synthesis of phosphonate functionalized alkene 5i: Following **GP1**, allyl bromide **85i** (563 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5i** (600 mg, 85%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (2H, s, g), 6.93 (1H, s, i), 5.50 (1H, d, $^{4}J_{P\text{-}H}$ = 5.5 Hz, H_e or $H_{e'}$), 5.33 (1H, d, $^{4}J_{P\text{-}H}$ = 5.5 Hz, H_e or $H_{e'}$), 4.09-3.95 (4H, m, b), 3.05 (2H, d, $^{2}J_{P\text{-}H}$ = 22 Hz, c), 2.32 (6H, s, j), 1.23 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.92 (d, $^{2}J_{C\text{-}P}$ = 4.5 Hz, d), 139.00 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, f), 137.82 (h), 129.49 (i), 124.33 (g), 116.89 (d, $^{3}J_{C\text{-}P}$ = 10.8 Hz, e), 62.09 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b), 33.15 (d, $^{1}J_{C\text{-}P}$ = 138.65, c), 21.49 (j), 16.43 (d, $^{3}J_{C\text{-}P}$ = 6.5 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.74 ppm; IR (neat) 2979 (aromatic C-H), 2910 (aliphatic C-H), 1599 (C=C), 1252 (P=O), 1053 (C-O), 1022 (C-O), 953 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{15}H_{23}O_3P$ = 282.1385, found 282.1380 *m/z*.

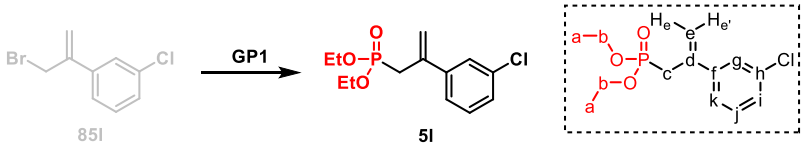


Synthesis of phosphonate functionalized alkene 5j: Following **GP1**, allyl bromide **85j** (538 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5j** (517 mg, 76%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.44 (2H, m, g), 7.06-7.00 (2H, m, h), 5.47 (1H, d, $^{4}J_{P\text{-}H}$ = 5.5 Hz, H_e or $H_{e'}$), 5.33 (1H, d, $^{4}J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 4.10-3.96 (4H, m, b), 3.04 (2H, d, $^{2}J_{P\text{-}H}$ = 22 Hz, c), 1.23 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.63 (d, $^{1}J_{C\text{-}F}$ = 245 Hz, i), 138.00 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, f), 136.97 (d, $^{2}J_{C\text{-}P}$ = 4 Hz, d), 128.21 (d, $^{3}J_{C\text{-}F}$ = 8 Hz, g), 117.31 (d, $^{3}J_{C\text{-}P}$ = 11 Hz, e), 115.27 (d, $^{2}J_{C\text{-}F}$ = 21 Hz, h), 62.20 (d, $^{2}J_{C\text{-}P}$ = 6 Hz, b), 33.45 (d, $^{1}J_{C\text{-}P}$ = 138 Hz, c), 16.49 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.28 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.75 ppm; IR (neat) 2982 (aromatic C-H), 2907 (aliphatic C-H),

1624 (C=C), 1601 (C=C), 1509 (C-F), 1249 (P=O), 1052 (C-O), 1022 (C-O), 902 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{13}H_{18}FO_3P$ = 272.0978, found 272.0982 *m/z*.

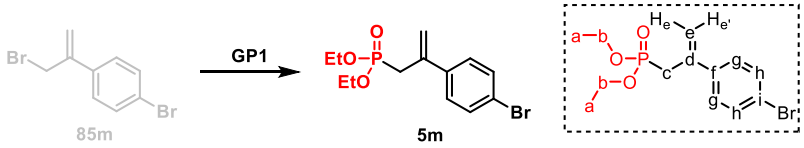


Synthesis of phosphonate functionalized alkene 5k: Following **GP1**, allyl bromide **85k** (579 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5k** (577 mg, 80%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.8 Hz, g or h), 7.29 (2H, d, *J* = 8.8 Hz, g or h), 5.50 (1H, d, $^4J_{P\text{-}H}$ = 5.5 Hz, H_e or $H_{e'}$), 5.35 (1H, d, $^4J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 4.06-3.96 (4H, m, b), 3.01 (2H, d, $^2J_{P\text{-}H}$ = 22.4 Hz, c), 1.21 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.23 (d, $^2J_{C\text{-}P}$ = 4 Hz, d), 137.87 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 133.72 (i), 128.52 (g or h), 127.78 (g or h), 117.79 (d, $^3J_{C\text{-}P}$ = 11 Hz, e), 62.17 (d, $^2J_{C\text{-}P}$ = 7 Hz, b), 33.17 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 16.44 (d, $^3J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.13 ppm; IR (neat) 2981 (aromatic C-H), 2905 (aliphatic C-H), 1623 (C=C), 1248 (P=O), 1022 (C-O), 940 (P-O), 835 (C-Cl) cm^{-1}; HRMS (EI) calculated for $C_{13}H_{18}ClO_3P$ = 288.0682, found 288.0690 *m/z*.

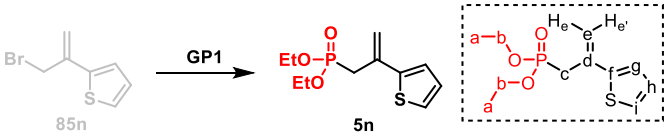


Synthesis of phosphonate functionalized alkene 5l: Following **GP1**, allyl bromide **85l** (579 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5l** (584 mg, 81%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (1H, dd, *J* = 2.0, 0.8 Hz, aryl), 7.39-7.34 (1H, m, aryl), 7.29-7.25 (2H, m, aryl), 5.53 (1H, dd, *J* = 5.5 ($^4J_{P\text{-}H}$), 0.4 ($^4J_{H\text{-}H}$) Hz, H_e or $H_{e'}$), 5.39 (1H, dd, *J* = 5.6 ($^4J_{P\text{-}H}$), 0.5 ($^4J_{H\text{-}H}$) Hz,

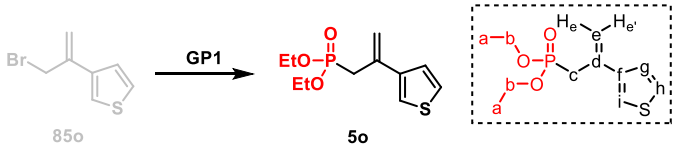
H_e or $H_{e'}$), 4.10-3.96 (4H, m, b), 3.03 (2H, dd, J = 22 ($^2J_{P\text{-}H}$), 0.8 ($^4J_{H\text{-}H}$) Hz, c), 1.23 (6H, t, J = 7.2 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.74 (d, $^2J_{C\text{-}P}$ = 4 Hz, d), 137.90 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 134.38 (h), 129.69 (aryl), 127.89 (aryl), 126.72 (aryl), 124.71 (aryl), 118.47 (d, $^3J_{C\text{-}P}$ = 11 Hz, e), 62.21 (d, $^2J_{C\text{-}P}$ = 7 Hz, b), 33.15 (d, $^1J_{C\text{-}P}$ = 139 Hz, c), 16.45 (d, $^3J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.96 ppm; IR (neat) 2981 (aromatic C-H), 2906 (aliphatic C-H), 1625 (C=C), 1248 (P=O), 1051 (C-O), 1021 (C-O), 960 (P-O), 788 (C-Cl) cm^{-1}; HRMS (EI) calculated for $C_{13}H_{18}ClO_3P$ = 288.0682, found 288.0691 *m/z*.



Synthesis of phosphonate functionalized alkene 5m: Following **GP1**, allyl bromide **85m** (690 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5m** (616 mg, 74%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (2H, d, J = 8.8 Hz, g or h), 7.36 (2H, d, J = 8.8 Hz, g or h), 5.52 (1H, d, $^4J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 5.37 (1H, d, $^4J_{P\text{-}H}$ = 5.6 Hz, H_e or $H_{e'}$), 4.10-3.96 (4H, m, b), 3.03 (2H, dd, J = 22.4 ($^2J_{P\text{-}H}$), 0.8 ($^4J_{H\text{-}H}$) Hz, c), 1.23 (6H, t, J = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.75 (d, $^2J_{C\text{-}P}$ = 4 Hz, d), 137.98 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 131.54 (g or h), 128.15 (g or h), 121.94 (i), 117.91 (d, $^3J_{C\text{-}P}$ = 11 Hz, e), 62.24 (d, $^2J_{C\text{-}P}$ = 7 Hz, b), 33.16 (d, $^1J_{C\text{-}P}$ = 139 Hz, c), 16.49 (d, $^3J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.15 ppm; IR (neat) 2980 (aromatic C-H), 2902 (aliphatic C-H), 1620 (C=C), 1248 (P=O), 1052 (C-O), 1021 (C-O), 955 (P-O), 759 (C-Br) cm^{-1}; HRMS (EI) calculated for $C_{13}H_{18}BrO_3P$ = 332.0177, found 332.0168 *m/z*.

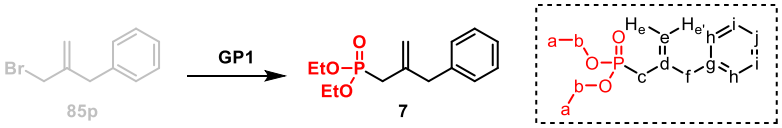


Synthesis of phosphonate functionalized alkene 5n: Following **GP1**, allyl bromide **85n** (508 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5n** (540 mg, 83%) as a light buff colored oil: TLC analysis (ethyl acetate) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (1H, d, *J* = 5.2 Hz, i), 7.15 (1H, d, *J* = 3.2 Hz, g), 7.00-6.98 (1H, m, h), 5.61 (1H, d, $^{4}J_{P\text{-}H}$ = 5.5 Hz, H_e or $H_{e'}$), 5.23 (1H, d, $^{4}J_{P\text{-}H}$ = 5.5 Hz, H_e or $H_{e'}$), 4.14-4.00 (4H, m, b), 3.05 (2H, d, $^{2}J_{P\text{-}H}$ = 22 Hz, c), 1.26 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.60 (d, $^{2}J_{C\text{-}P}$ = 5 Hz, d), 132.33 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, f), 127.63 (h), 125.05 (g), 124.98 (i), 115.56 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, e), 62.38 (d, $^{2}J_{C\text{-}P}$ = 6 Hz, b), 33.46 (d, $^{1}J_{C\text{-}P}$ = 139 Hz, c), 16.53 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.85 ppm; IR (neat) 3091 (aromatic C-H), 2980 (aliphatic C-H), 1622 (C=C), 1247 (P=O), 1051 (C-O), 1020 (C-O/C=S), 954 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{11}H_{17}O_3PS$ = 260.0636, found 260.0630 *m/z*.

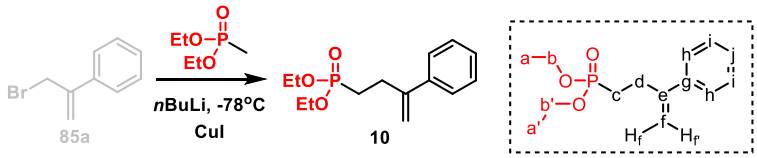


Synthesis of phosphonate functionalized alkene 5o: Following **GP1**, allyl bromide **85o** (508 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **5o** (555 mg, 85%) as a light buff oil: TLC analysis (ethyl acetate) R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, s, i), 7.28-7.25 (2H, m, g+h), 5.57 (1H, d, $^{4}J_{P\text{-}H}$ = 5.5 Hz, H_e or $H_{e'}$), 5.28 (1H, d, $^{4}J_{P\text{-}H}$ = 5.5 Hz, H_e or $H_{e'}$), 4.12-4.98 (4H, m, b), 3.02 (2H, d, $^{2}J_{P\text{-}H}$ = 22 Hz, c), 1.25 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.96 (d, $^{2}J_{C\text{-}P}$ = 4 Hz, d), 133.37 (d, $^{3}J_{C\text{-}P}$ = 11 Hz, f), 125.94 (g or h), 125.77 (g or h), 121.97 (i), 115.87 (d, $^{3}J_{C\text{-}P}$ = 11 Hz, e), 62.27 (d, $^{2}J_{C\text{-}P}$ = 7 Hz, b), 33.59 (d, $^{1}J_{C\text{-}P}$ = 138 Hz, c), 16.49 (d, $^{3}J_{C\text{-}P}$ = 7 Hz, a) ppm; ^{31}P NMR (162

MHz, $CDCl_3$) δ 26.63 ppm; IR (neat) 3090 (aromatic C-H), 2978 (aliphatic C-H), 1621 (C=C), 1250 (P=O), 1052 (C-O), 1020 (C-O/C=S), 955 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{11}H_{17}O_3PS$ = 260.0636, found 260.0630 *m/z*.



Synthesis of phosphonate functionalized alkene 7: Following **GP1**, allyl bromide **85p** (527 mg, 2.50 mmol, 1.00 eq) yields the alkene substrate **7** (543 mg, 81%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.21 (5H, m, aryl), 5.06 (1H, d, $^4J_{P-H}$ = 5.2 Hz, H_e or $H_{e'}$), 4.98 (1H, d, $^4J_{P-H}$ = 5.2 Hz, H_e or $H_{e'}$), 4.17-4.08 (4H, m, b), 3.53 (2H, s, f), 2.52 (2H, d, $^2J_{P-H}$ = 22 Hz, c), 1.33 (6H, t, *J* = 7.2 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.60 (d, $^2J_{C-P}$ = 11 Hz, d), 138.94 (g), 129.29 (aryl), 128.51 (aryl), 126.46 (aryl), 116.50 (d, $^3J_{C-P}$ = 11 Hz, e), 62.00 (d, $^2J_{C-P}$ = 7 Hz, b), 43.40 (d, $^3J_{C-P}$ = 4 Hz, f), 32.91 (d, $^1J_{C-P}$ = 137 Hz, c), 16.56 (d, $^3J_{C-P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.02 ppm; IR (neat) 2981 (aromatic C-H), 2904 (aliphatic C-H), 1645 (C=C), 1247 (P=O), 1052 (C-O), 1023 (C-O), 956 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{14}H_{21}O_3P$ = 268.1228, found 268.1231 *m/z*.



Synthesis of homoallylic phosphonate substrate 10: This synthesis was carried out according to our previously reported procedure.[6] Allyl bromide **85a** (492 mg, 2.50 mmol, 1.10 eq) yields the homoallylic phosphonate **10** (470 mg, 70%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (5H, m, aryl), 5.32 (1H, s, H_f or $H_{f'}$), 5.12 (1H, d, $^4J_{H-H}$ = 1.0 Hz, H_f or $H_{f'}$), 4.14-4.07 (4H, m,

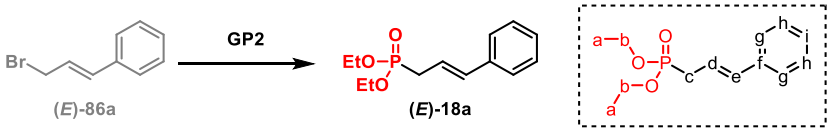
b), 2.84-2.78 (2H, m, d), 1.94-1.85 (2H, m, c), 1.34 (6H, t, J = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.45 (d, $^{3}J_{C-P}$ = 19 Hz, e), 140.27 (g), 128.60 (aryl), 127.84 (aryl), 126.23 (aryl), 112.76 (f), 61.70 (d, $^{2}J_{C-P}$ = 7 Hz, b), 28.29 (d, $^{2}J_{C-P}$ = 4 Hz, d), 24.96 (d, $^{1}J_{C-P}$ = 140 Hz, c), 16.64 (d, $^{3}J_{C-P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.46 ppm; IR (neat) 3082 (aromatic C-H), 2980 (aliphatic C-H), 1629 (C=C), 1243 (P=O), 1054 (C-O), 1024 (C-O), 958 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{14}H_{21}O_3P$ = 268.1228, found 268.1232 *m/z*.

Synthesis of 1,2-disubstituted vinyl arene substrates

Substitution of the corresponding allyl bromides (GP2): Synthesis of allyl phosphonates via substitution of the corresponding allyl bromides is carried out as follows. A 2.0M solution of NaHMDS (1.1 equiv.) is added drop-wise to a solution of diethyl phosphite (1.0 equiv.) in anhydrous THF (0.5 M) at 0 ºC. The resultant mixture is stirred at room temperature for 10 minutes. A solution of the corresponding allyl bromide (1.1 equiv.) in THF (0.5 M) is added dropwise to the mixture over 10 minutes (room temperature). The completion of the reaction mixture (*ca.* 1-2 hours) is determined by analysis of unworked up reaction samples by ^{31}P NMR spectrum following disappearance of $HP{=}O(OEt)_2$ peak at ~8 ppm and appearance of a new peak in the range of 25-30 ppm for the substrate. After complete reaction, the resulting mixture is filtered through a celite bed and the bed washed with ethyl acetate. The combined filtrates are concentrated under reduced pressure and purification is carried out using silica gel chromatography.

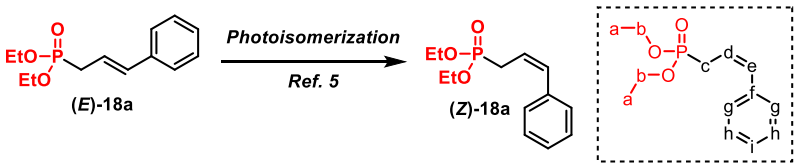
Synthesis of allyl phosphonates via palladium-catalyzed substitution of the corresponding allyl carbonates (GP3): The synthesis of substrates via Palladium-

catalyzed allylic substitution of the corresponding allyl carbonates is carried out with few modifications of the original procedure reported by Zhao[7] and co-workers as follows. Under a dry nitrogen atmosphere, a mixture of $Pd_2(dba)_3$ (2 mol%) and Xantphos (4 mol%) in dry THF is stirred for 1 hour. To the resultant palladium-complex solution, a mixture of the corresponding allyl carbonate (1 equiv.) and diethyl phosphite (1.2 equiv.) is added and the resultant mixture is refluxed for 24 hours. Afterwards, the reaction mixture is cooled down to room-temperature and filtered over a bed of celite. The celite bed is washed with ethyl-acetate and the combined filtrates are concentrated under reduced pressure. Purification is carried out using silica-gel chromatography. **Note: *GP3*** *is carried out for the preparation of substrates bearing a basic nitrogen or sensitive heterocyclic functional groups. In such cases either the preparation of corresponding allyl bromide isn't straightforward, or the corresponding allyl bromides are very unstable.*

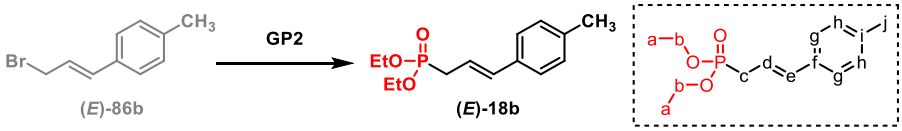


Synthesis of allylic phosphonate (*E*)-18a: Following **GP2**, the allyl bromide (*E*)-**86a** (197 mg, 1.00 mmol) yields alkene substrate (*E*)-**18a** (218 mg, 86%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 7.5 Hz, g), 7.31-7.27 (2H, m, aryl), 7.23-7.19 (1H, m, aryl), 6.52 (1H, dd, *J* = 15.8, 5.1 Hz, e), 6.21-6.12 (1H, m, d), 4.18-4.05 (4H, m, b), 2.76 (2H, ddd, *J* = 22.4, 7.5, 1.3 Hz, c), 1.31 (6H, t, *J* = 7.08 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.88 (d, $^4J_{C\text{-}P}$ = 3.5 Hz, f), 134.73 (d, $^3J_{C\text{-}P}$ = 14.79 Hz, e), 128.61 (aryl), 127.64 (aryl), 126.28 (d, $^5J_{C\text{-}P}$ = 2.07 Hz, g), 118.91 (d, $^2J_{C\text{-}P}$ = 12.0 Hz, d), 62.08 (d, $^2J_{C\text{-}P}$ = 6.7 Hz, b), 31.16 (d, $^1J_{C\text{-}P}$ = 139.89 Hz, c), 16.55 (d, $^3J_{C\text{-}P}$ = 5.89 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.81 ppm; IR (neat)

3055 (sp^2 C-H), 2979 (sp^3 C-H), 1651 (C=C), 1597 (C=C), 1495 (aromatic C=C), 1448 (aromatic C=C), 1247 (P=O), 1018 (C-O), 955 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{19}O_3P+Na^+$ = 277.0972, found 277.0972 *m/z*.

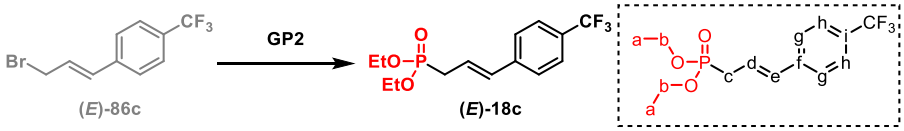


Synthesis of allylic phosphonate (*Z*)-18a: Photoisomerization of the allylic phosphonate (*E*)-**18a** (200 mg, 0.79 mmol; Ref. **5**) yields the diastereomeric substrate (*Z*)-**18a** (178 mg, 89%; Z:E ratio = 9:1) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.21 (5H, m, aryl), 6.67-6.63 (1H, m, e), 5.76-5.68 (1H, m, d), 4.13-4.04 (4H, m, b), 2.84 (2H, ddd, *J* = 22.4, 8.0, 1.5 Hz, c), 1.29 (6H, t, *J* = 7 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.40 (d, $^4J_{C\text{-}P}$ = 3.5 Hz, f), 133.17 (d, $^3J_{C\text{-}P}$ = 14.5 Hz, e), 128.59 (d, $^5J_{C\text{-}P}$ = 2.0 Hz, g), 128.39 (h), 127.21 (i), 120.45 (d, $^2J_{C\text{-}P}$ = 11 Hz, d), 61.98 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b), 26.93 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 16.45 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.28 ppm; IR (neat) 3025 (sp^2 C-H), 2904 (sp^3 C-H), 1599 (C=C), 1495 (aromatic C=C), 1446 (aromatic C=C), 1247 (P=O), 1021 (C-O), 955 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{19}O_3P+Na^+$ = 277.0970, found 277.0971 *m/z*.



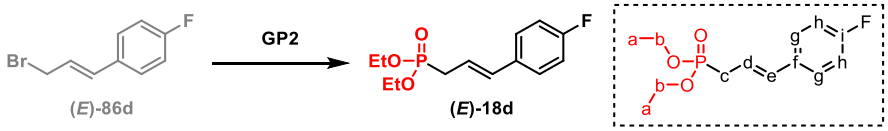
Synthesis of allylic phosphonate (*E*)-18b: Following **GP2**, the allyl bromide (*E*)-**86b** (211 mg, 1.00 mmol) yields alkene substrate (*E*)-**18b** (244 mg, 91%) as a colorless oil:

TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.70 Hz, g), 7.13 (2H, d, *J* = 7.98 Hz, h), 6.51 (1H, dd, *J* = 15.79, 5.15 Hz, e), 6.17-6.08 (1H, m, d), 4.20-4.07 (4H, m, b), 2.76 (2H, ddd, *J* = 22.7, 7.6, 1.18 Hz, c), 2.34 (3H, s, j), 1.33 (6H, t, *J* = 7.06 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.57 (d, $^{7}J_{C\text{-}P}$ = 1.07 Hz, i), 134.71 (d, $^{3}J_{C\text{-}P}$ = 14.93 Hz, e), 134.23 (d, $^{4}J_{C\text{-}P}$ = 3.3 Hz, f), 129.41 (h), 126.29 (d, $^{5}J_{C\text{-}P}$ = 2.05 Hz, g), 117.86 (d, $^{2}J_{C\text{-}P}$ = 12.09 Hz, d), 62.19 (d, $^{2}J_{C\text{-}P}$ = 6.65 Hz, b), 31.25 (d, $^{1}J_{C\text{-}P}$ = 139.92 Hz, c), 21.34 (j), 16.65 (d, $^{3}J_{C\text{-}P}$ = 5.94 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.02 ppm; IR (neat) 2980 (C-H), 1513 (C=C), 1443 (aromatic C=C), 1391 (aromatic C=C), 1247 (P=O), 1019 (C-O), 957 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{21}O_3P+Na^+$ = 291.1129, found 291.1126 *m/z*.

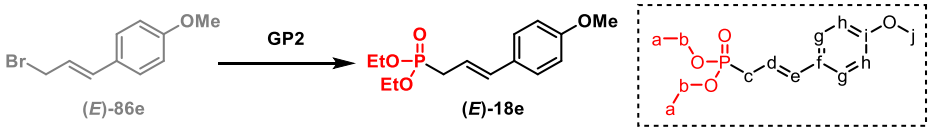


Synthesis of allylic phosphonate (*E*)-18c: Following **GP2**, the allyl bromide (*E*)-**86c** (265 mg, 1.00 mmol) yields alkene substrate (*E*)-**18c** (164 mg, 51%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 8.25 Hz, g), 7.46 (2H, d, *J* = 8.15 Hz, h), 6.57 (1H, dd, *J* = 15.5, 5.10 Hz, e), 6.34-6.24 (1H, m, d), 4.22-4.08 (4H, m, b), 2.80 (2H, ddd, *J* = 22.5, 7.6, 1.2 Hz, c), 1.34 (6H, t, *J* = 7.05 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.38 (f), 133.52 (d, $^{3}J_{C\text{-}P}$ = 14.5 Hz, e), 129.57 (q, $^{2}J_{C\text{-}F}$ = 32.5 Hz, i), 126.55 (d, *J* = 2 Hz, g), 125.71 (q, $^{3}J_{C\text{-}F}$ = 3.5 Hz, h), 124.50 (q, $^{1}J_{C\text{-}F}$ = 272 Hz, CF_3), 122.07 (d, $^{2}J_{C\text{-}P}$ = 11.93 Hz, d), 62.30 (d, $^{2}J_{C\text{-}P}$ = 6.70 Hz, b), 31.36 (d, $^{1}J_{C\text{-}P}$ = 139 Hz, c), 16.65 (d, $^{3}J_{C\text{-}P}$ = 5.78 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.23 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.54 ppm; IR (neat) 2983 (sp^2 C-H), 2933

(sp^3 C-H), 1614 (C=C), 1323 (C-F), 1247 (P=O), 1162 (C-O), 1015 (C-O), 953 (P-O), 789 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{18}F_3O_3P+Na^+$ = 345.0843, found 345.0849 *m/z*.

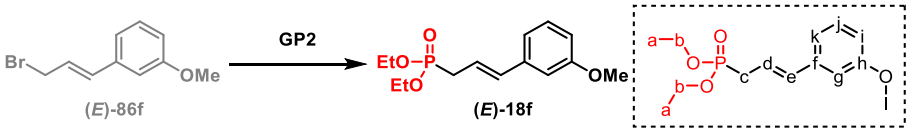


Synthesis of allylic phosphonate (*E*)-18d: Following **GP2**, the allyl bromide (*E*)-**86d** (215 mg, 1.00 mmol) yields alkene substrate (*E*)-**18d** (180 mg, 66%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.28 (2H, m, g), 7.01-6.97 (2H, m, h), 6.49 (1H, dd, *J* = 15.0, 5.5 Hz, e), 6.13-6.03 (1H, m, d), 4.20-4.04 (4H, m, b), 2.75 (2H, ddd, *J* = 22.25, 7.5, 1.0 Hz, c), 7.06 (6H, t, *J* = 7.05 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.45 (d, $^1J_{C\text{-}F}$ = 246 Hz, i), 133.62 (d, $^3J_{C\text{-}P}$ = 14.9 Hz, e), 127.89 (dd, $^3J_{C\text{-}F}$ = 8.0 Hz, $^6J_{C\text{-}P}$ = 2.0 Hz, g), 118.77 (dd, $^2J_{C\text{-}P}$ = 12 Hz, $^6J_{C\text{-}F}$ = 2.0 Hz, d), 115.62 (d, $^2J_{C\text{-}F}$ = 21.9 Hz, h), 62.20 (d, $^2J_{C\text{-}P}$ = 6.75 Hz, b), 31.18 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 16.64 (d, $^3J_{C\text{-}P}$ = 5.9 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.77 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.49 ppm; IR (neat) 2981 (sp^2 C-H), 2909 (sp^3 C-H), 1600 (C=C), 1508 (C-F), 1247 (P=O), 1225 (P=O), 1020 (C-O), 957 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{18}FO_3P+Na^+$ = 295.0875, found 295.0885 *m/z*.

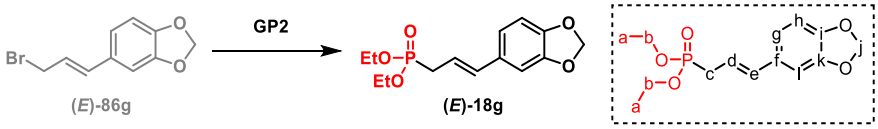


Synthesis of allylic phosphonate (*E*)-18e: Following **GP2**, the allyl bromide (*E*)-**86e** (227 mg, 1.00 mmol) yields alkene substrate (*E*)-**18e** (202 mg, 71%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.5 Hz, g), 6.85 (2H, d, *J* = 8.5 Hz, h), 6.48 (1H, dd, *J* = 15.0, 5.5 Hz, e), 6.08-5.98 (1H,

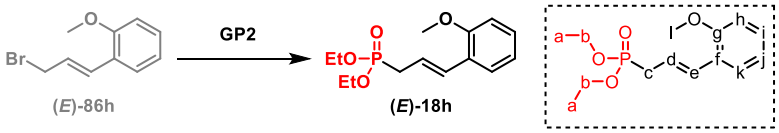
m, d), 4.21-4.08 (4H, m, b), 3.81 (3H, s, j), 2.75 (2H, ddd, J = 22.0, 7.5, 1.25 Hz, c), 1.33 (6H, t, J = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.36 (i), 134.22 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 129.84 (d, $^{4}J_{C\text{-}P}$ = 3.5 Hz, f), 127.55 (d, $^{5}J_{C\text{-}P}$ = 2.0 Hz, g), 116.59 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 114.12 (h), 62.16 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b), 55.44 (j), 31.20 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 16.65 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.15 ppm; IR (neat) 2980 (sp^2 C-H), 2905 (sp^3 C-H), 1606 (C=C), 1510, 1244 (P=O), 1018 (C-O), 958 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{21}O_4P$+Na^+ = 307.1075, found 307.1078 *m/z*.



Synthesis of allylic phosphonate (*E*)-18f: Following **GP2**, the allyl bromide (*E*)-**86f** (227 mg, 1.00 mmol) yields alkene substrate (*E*)-**18f** (196 mg, 69%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.17 (1H, m, j), 6.93 (2H, d, J = 7.6 Hz, k), 6.87 (1H, s, g), 6.76 (1H, d, J = 8.2 Hz, i), 6.47 (1H, dd, J = 15.75, 4.75 Hz, e), 6.19-6.09 (1H, m, d), 4.16-4.04 (4H, m, b), 3.77 (3H, s, l), 2.73 (2H, dd, J = 22.5, 7.5 Hz, c), 1.30 (6H, td, J = 7.0, 2.5 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.82 (h), 138.28 (d, $^{4}J_{C\text{-}P}$ = 3.5 Hz, f), 134.62 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 129.56 (j), 119.19 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 118.95 (d, $^{5}J_{C\text{-}P}$ = 1.65 Hz, k), 113.25 (i), 111.56 (d, $^{5}J_{C\text{-}P}$ = 2.0 Hz, g), 62.08 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b), 55.22 (l), 31.08 (d, $^{1}J_{C\text{-}P}$ = 139 Hz, c), 16.51 (d, $^{3}J_{C\text{-}P}$ = 5.9 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.75 ppm; IR (neat) 2981 (sp^2 C-H), 2905 (sp^3 C-H), 1597 (C=C), 1488 (aromatic C=C), 1463 (aromatic C=C), 1241 (P=O), 1019 (C-O), 957 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{21}O_4P$+Na^+ = 307.1075, found 307.1077 *m/z*.

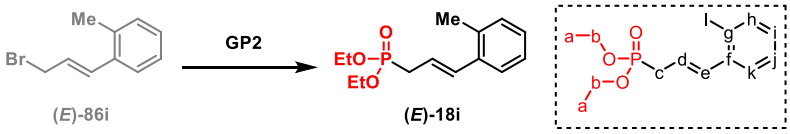


Synthesis of allylic phosphonate (*E*)-18g: Following **GP2**, the allyl bromide (*E*)-**86g** (240 mg, 1.00 mmol) yields alkene substrate (*E*)-**18g** (206 mg, 69%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (1H, s, l), 6.80-6.74 (2H, m, g+h), 6.44 (1H, dd, *J* = 15.5, 5.5 Hz, e), 6.04-5.95 (3H, m, d+j), 4.22-4.04 (4H, m, b), 2.74 (2H, ddd, *J* = 22.0, 7.5, 1.5 Hz, c), 1.33 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.18 (i), 147.37 (d, $^6J_{C\text{-}P}$ = 1.0 Hz, k), 134.39 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 131.51 (d, $^4J_{C\text{-}P}$ = 3.5 Hz, f), 121.02 (d, $^5J_{C\text{-}P}$ = 2.25 Hz, g), 117.11 (d, $^2J_{C\text{-}P}$ = 12 Hz, d), 108.42 (h), 105.74 (d, $^5J_{C\text{-}P}$ = 2.0 Hz, l), 101.24 (j), 62.20 (d, $^2J_{C\text{-}P}$ = 6.75 Hz, b), 31.12 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 16.66 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.99 ppm; IR (neat) 2980 (sp^2 C-H), 2904 (sp^3 C-H), 1605 (C=C), 1489 (aromatic C=C), 1445 (aromatic C=C), 1240 (P=O), 1018 (C-O), 957 (P-O), 781 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{19}O_5P+Na^+$ = 321.0868, found 321.0869 *m/z*.

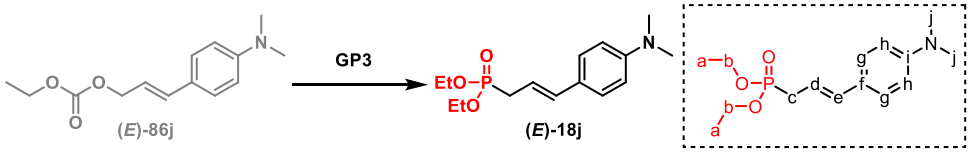


Synthesis of allylic phosphonate (*E*)-18h: Following **GP2**, the allyl bromide (*E*)-**86h** (227 mg, 1.00 mmol) yields alkene substrate (*E*)-**18h** (169 mg, 63%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, t, *J* = 8.0 Hz, aryl), 6.97 (1H, d, *J* = 7.6 Hz, k), 6.91 (1H, br s, h), 6.81 (1H, dd, *J* = 8.25, 2.50 Hz, aryl), 6.52 (1H, dd, *J* = 15.0, 5.5 Hz, e), 6.23-6.14 (1H, m, d), 4.19-4.09 (4H, m, b), 3.83 (3H, s, l), 2.78 (2H, ddd, *J* = 22, 7.5, 1.5 Hz, c), 1.34 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR

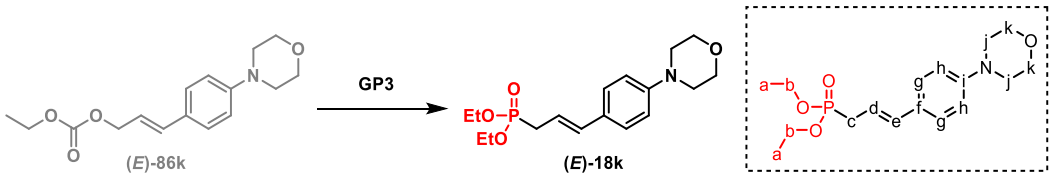
(100 MHz, $CDCl_3$) δ 159.98 (g), 138.45 (d, $^4J_{C\text{-}P}$ = 3.5 Hz, f), 134.72 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 129.72 (aryl), 119.38 (d, $^2J_{C\text{-}P}$ = 12 Hz, d), 119.13 (d, $^5J_{C\text{-}P}$ = 2.0 Hz, k), 113.41 (aryl), 111.73 (d, $^6J_{C\text{-}P}$ = 2.0 Hz, h), 62.26 (d, $^2J_{C\text{-}P}$ = 6.75 Hz, b), 55.42 (l), 31.28 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 16.68 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.78 ppm; IR (neat) 2980 (sp^2 C-H), 2904 (sp^3 C-H), 1597 (C=C), 1578 (C=C), 1247 (P=O), 1156 (C-O), 1019 (C-O), 956 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{21}O_4P+Na^+$ = 307.1075, found 307.1078 *m/z*.



Synthesis of allylic phosphonate (*E*)-18i: Following **GP2**, the allyl bromide (*E*)-**86i** (211 mg, 1.00 mmol) yields alkene substrate (*E*)-**18i** (177 mg, 66%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.40 (1H, m, aryl), 7.23-7.11 (3H, m, aryl), 6.74 (1H, d, *J* = 15.5, 5.5 Hz, e), 6.08-5.99 (1H, m, d), 4.19-4.06 (4H, m, b), 2.79 (2H, dd, *J* = 22.0, 7.50 Hz, c), 2.33 (3H, s, l), 1.33 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.06 (d, $^4J_{C\text{-}P}$ = 3.5 Hz, f), 135.18 (d, $^5J_{C\text{-}P}$ = 2.0 Hz, g), 132.70 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 130.26 (aryl), 127.56 (aryl), 126.16 (aryl), 125.74 (d, $^5J_{C\text{-}P}$ = 2.5 Hz, k), 120.22 (d, $^2J_{C\text{-}P}$ = 12 Hz, d), 62.06 (d, $^2J_{C\text{-}P}$ = 6.75 Hz, b), 31.37 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 19.82 (l), 16.54 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.88 ppm; IR (neat) 2979 (sp^2 C-H), 2906 (sp^3 C-H), 1694 (C=C), 1483 (aromatic C=C), 1391 (aromatic C=C), 1247 (P=O), 1019 (C-O), 958 (P-O), 746 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{21}O_3P+Na^+$ = 291.1126, found 291.1129 *m/z*.

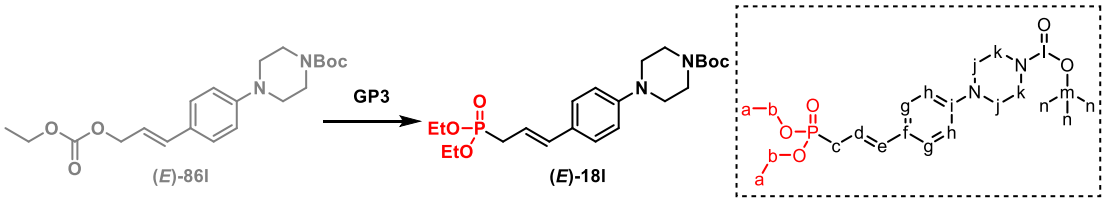


Synthesis of allylic phosphonate (*E*)-18j: Following **GP3**, the allyl carbonate (*E*)-**86j** (249 mg, 1.00 mmol) yields alkene substrate (*E*)-**18j** (110 mg, 37%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 9 Hz, g), 6.69 (2H, d, *J* = 9 Hz, h), 6.45 (1H, dd, *J* = 15.75, 5.5 Hz, e), 6.01-5.92 (1H, m, d), 4.20-4.07 (4H, m, b), 2.97 (6H, s, j), 2.76 (2H, ddd, *J* = 22, 7.5, 1.5 Hz, c), 1.33 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.25 (i), 134.70 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 127.36 (d, $^5J_{C\text{-}P}$ = 1.6 Hz, g), 125.62 (d, $^4J_{C\text{-}P}$ = 3.3 Hz, f), 114.19 (d, $^2J_{C\text{-}P}$ = 12 Hz, d), 112.53 (h), 62.17 (d, $^2J_{C\text{-}P}$ = 6.8 Hz, b), 40.67 (j), 31.27 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 16.68 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.50 ppm; IR (neat) 2980 (sp^2 C-H), 2902 (sp^3 C-H), 1608 (C=C), 1520, 1352 (C-N), 1246 (P=O), 1019 (C-O), 944 (P-O), 786 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{24}NO_3P$+Na^+ = 320.1391, found 320.1398 *m/z*.

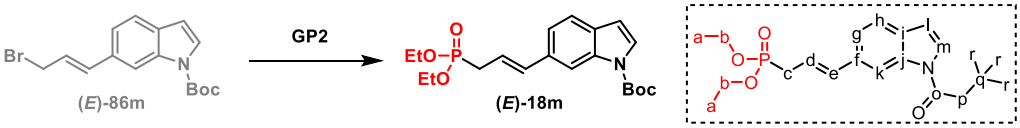


Synthesis of allylic phosphonate (*E*)-18k: Following **GP3**, the allyl carbonate (*E*)-**86k** (291 mg, 1.00 mmol) yields alkene substrate (*E*)-**18k** (139 mg, 41%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (2H, d, *J* = 8.5 Hz, g), 6.85 (2H, d, *J* = 8.5 Hz, h), 6.46 (1H, dd, *J* = 15.5, 5.5 Hz, e), 6.10-5.93 (1H, m, d), 4.18-4.06 (4H, m, b), 3.85 (4H, t, *J* = 4.5 Hz, k), 3.16 (4H, t, *J* = 4.5 Hz, j), 2.75 (2H, dd, *J* = 22.0, 7.5 Hz, c), 1.32 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.79

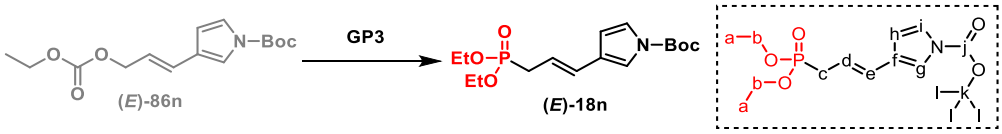
(i), 134.29 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 128.83 (d, $^{4}J_{C\text{-}P}$ = 3.5, f), 127.28 (d, $^{5}J_{C\text{-}P}$ = 2.0 Hz, g), 115.99 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 115.52 (h), 66.95 (k), 62.13 (d, $^{2}J_{C\text{-}P}$ = 6.7 Hz, b), 49.18 (j), 31.18 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 16.62 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.23 ppm; IR (neat) 2976 (sp^2 C-H), 2823 (sp^3 C-H), 1605 (C=C), 1514, 1449 (aromatic C=C), 1379 (aromatic C=C/C-N), 1234 (P=O), 1120 (C-O), 925 (P-O), 787 cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{26}NO_4P+Na^+$ = 362.1497, found 362.1498 *m/z*.



Synthesis of allylic phosphonate (*E*)-18l: Following **GP3**, the allyl carbonate (*E*)-**86l** (195 mg, 0.50 mmol) yields alkene substrate (*E*)-**18l** (99 mg, 45%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.75 Hz, g), 6.85 (2H, d, *J* = 8.75 Hz, h), 6.43 (1H, dd, *J* = 15.5, 5.5 Hz, e), 6.05-5.93 (1H, m, d), 4.17-4.04 (4H, m, b), 3.56 (4H, d, *J* = 5.0 Hz, j or k), 3.13 (4H, d, *J* = 5.0 Hz, j or k), 2.73 (2H, ddd, *J* = 22, 7.5, 1.0 Hz, c), 1.47 (9H, s, n), 1.30 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.79 (l), 150.71 (i), 134.25 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 128.96 (d, $^{4}J_{C\text{-}P}$ = 3.5 Hz, f), 127.25 (d, $^{5}J_{C\text{-}P}$ = 1.8 Hz, g), 116.35 (h), 116.06 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 80.00 (m), 62.11 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz, b), 49.17 (j or k), 43.58 (j or k), 31.14 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 28.52 (n), 16.59 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.21 ppm; IR (neat) 2979 (sp^2 C-H), 2904 (sp^3 C-H), 1691 (C=O), 1606 (C=C), 1514, 1233 (P=O), 1162 (C-O), 1020 (C-O), 961 (P-O), 751 cm^{-1}; HRMS (ESI) calculated for $C_{22}H_{35}N_2O_5P+Na^+$ = 461.2181, found 461.2180 *m/z*.

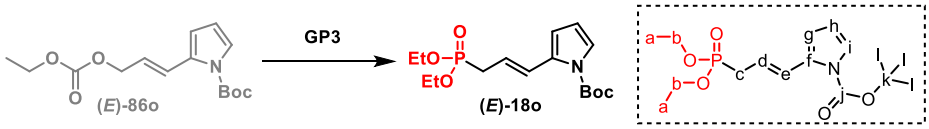


Synthesis of allylic phosphonate (*E*)-18m: Following **GP2**, the allyl bromide (*E*)-**86m** (168 mg, 0.50 mmol) yields alkene substrate (*E*)-**18m** (153 mg, 80%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (1H, s, k), 7.58 (1H, d, *J* = 3.6 Hz, m), 7.49 (1H, d, *J* = 8.0 Hz, h), 7.30 (1H, d, *J* = 8.0 Hz, g), 6.65 (1H, dd, *J* = 15.5, 5.5 Hz, e), 6.54 (1H, dd, *J* = 3.6, 0.5 Hz, l), 6.27-6.17 (1H, m, d), 4.21-4.08 (4H, m, b), 2.81 (2H, ddd, *J* = 22.0, 7.5, 1.5 Hz, c), 1.69 (9H, s, r), 1.34 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.87 (o), 135.78 (i or j), 135.66 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 133.49 (d, $^{4}J_{C\text{-}P}$ = 3.5 Hz, f), 130.32 (i or j), 126.56 (m), 121.22 (d, $^{5}J_{C\text{-}P}$ = 2.0 Hz, g), 121.05 (h), 117.92 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 113.49 (d, $^{5}J_{C\text{-}P}$ = 2.0 Hz, k), 107.41 (l), 83.91 (q), 62.22 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b), 31.38 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 28.37 (r), 16.68 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.05 ppm; IR (neat) 2979 (sp^2 C-H), 2904 (sp^3 C-H), 1729 (C=O), 1612 (C=C), 1335 (C-N), 1250 (P=O), 1125 (C-O), 1020 (C-O), 960 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{20}H_{28}NO_5P+Na^+$ = 416.1603, found 416.1607 *m/z*.

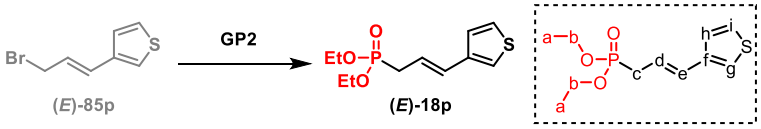


Synthesis of allylic phosphonate (*E*)-18n: Following **GP3**, the allyl carbonate (*E*)-**86n** (295 mg, 1.00 mmol) yields alkene substrate (*E*)-**18n** (151 mg, 44%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.15 (2H, m, g+i), 6.40-6.35 (2H, m, e+h), 5.94-5.85 (1H, m, d), 4.19-4.06 (4H, m, b), 2.72 (2H,

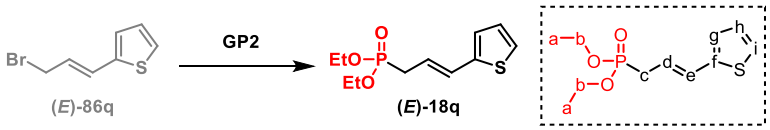
dd, J = 22, 7.5 Hz, c), 1.60 (9H, s, l), 1.33 (6H, t, J = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.89 (j), 127.15 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 125.51 (d, $^{4}J_{C\text{-}P}$ = 3.75 Hz, f), 121.17 (i), 117.88 (d, $^{5}J_{C\text{-}P}$ = 3 Hz, g), 117.29 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 109.57 (h), 83.93 (k), 62.20 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b), 31.16 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 28.17 (l), 16.67 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.13 ppm; IR (neat) 2980 (sp^2 C-H), 2802 (sp^3 C-H), 1738 (C=O), 1352 (C-N), 1251 (P=O), 1154 (C-O), 1021 (C-O), 959 (P-O), 769 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{26}NO_5P$+Na^+ = 366.1446, found 366.1446 *m/z*.



Synthesis of allylic phosphonate (*E*)-18o: Following **GP3**, the allyl carbonate (*E*)-**86o** (295 mg, 1.00 mmol) yields alkene substrate (*E*)-**18o** (134 mg, 39%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, br s, i), 7.10 (1H, dd, J = 15.5, 5.5 Hz, e), 6.38 (1H, br s, g), 6.12 (1H, dd, J = 3.5, 3.0 Hz, h), 5.99-5.90 (1H, m, d), 4.19-4.07 (4H, m, b), 2.76 (2H, dd, J = 22.0, 7.5 Hz, c), 1.60 (9H, s, l), 1.33 (6H, t, J = 7.10 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.51 (j), 133.58 (d, $^{4}J_{C\text{-}P}$ = 3.75 Hz, f), 125.98 (d, $^{3}J_{C\text{-}P}$ = 16 Hz, e), 121.87 (i), 118.70 (d, $^{2}J_{C\text{-}P}$ = 12.25 Hz, d), 111.12 (d, $^{5}J_{C\text{-}P}$ = 3.0 Hz, g), 111.00 (h), 83.96 (k), 62.19 (d, $^{2}J_{C\text{-}P}$ = 6.75 Hz, b), 31.34 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 28.18 (l), 16.65 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.85 ppm; IR (neat) 2979 (sp^2 C-H), 2906 (sp^3 C-H), 1739 (C=O), 1320 (C-N), 1246 (P=O), 1122 (C-O), 1022 (C-O), 958 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{26}NO_5P$+Na^+ = 366.1446, found 366.1447 *m/z*.

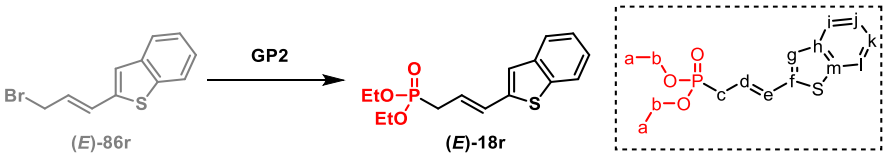


Synthesis of allylic phosphonate (*E*)-18p: Following **GP2**, the allyl bromide (*E*)-**85p** (203 mg, 1.00 mmol) yields alkene substrate (*E*)-**18p** (216 mg, 83%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, dd, *J* = 5.0, 3.0 Hz, h), 7.20 (1H, d, *J* = 5.0 Hz, i), 7.12 (1H, br s, g), 6.54 (1H, dd, *J* = 15.75, 5.5 Hz, e), 6.07-5.97 (1H, m, d), 4.19-4.06 (4H, m, b), 2.72 (2H, ddd, *J* = 22, 7.5, 1.0 Hz, c), 1.32 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.57 (d, $^{4}J_{C\text{-}P}$ = 3.5 Hz, f), 129.02 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 126.16 (h), 125.05 (i), 121.98 (d, $^{5}J_{C\text{-}P}$ = 3.0 Hz, g), 118.76 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 62.16 (d, $^{2}J_{C\text{-}P}$ = 6.7 Hz, b), 31.09 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 16.63 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.88 ppm; IR (neat) 3078 (sp^2 C-H), 2904 (sp^3 C-H), 1477 (aromatic C=C), 1390 (aromatic C=C), 1244 (P=O), 1018 (C-O), 955 (P-O), 765 cm^{-1}; HRMS (ESI) calculated for $C_{11}H_{17}O_3PS+Na^+$ = 283.0534, found 283.0534 *m/z*.

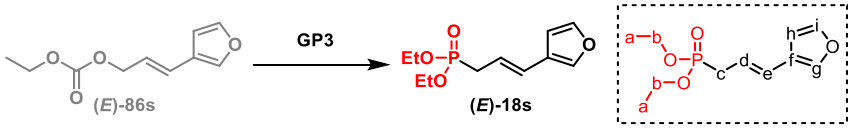


Synthesis of allylic phosphonate (*E*)-18q: Following **GP2**, the allyl bromide (*E*)-**86q** (203 mg, 1.00 mmol) yields alkene substrate (*E*)-**18q** (205 mg, 79%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (1H, m, g or h), 6.96-6.93 (2H, m, g *or* h *and* i), 6.66 (1H, dd, *J* = 15.5, 5.5 Hz, e), 6.04-5.94 (1H, m, d), 4.19-4.06 (4H, m, b), 2.73 (2H, ddd, *J* = 22, 7.5, 1.5 Hz, c), 1.35-1.31 (6H, m, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.94 (d, $^{4}J_{C\text{-}P}$ = 4.5 Hz, f), 127.90 (d, $^{3}J_{C\text{-}P}$ = 15

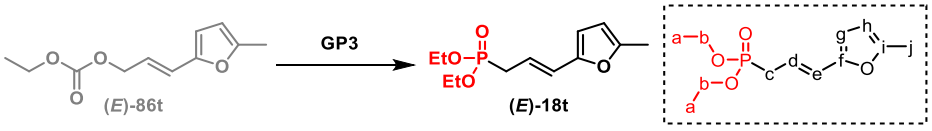
Hz, e), 127.44 (i), 125.55 (d, $^{5}J_{C\text{-}P}$ = 3.0 Hz, g), 124.31 (d, $^{6}J_{C\text{-}P}$ = 1.5 Hz), 118.57 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 62.25 (d, $^{2}J_{C\text{-}P}$ = 6.7 Hz, b), 31.06 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 16.64 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.45 ppm; IR (neat) 3030 (sp^2 C-H), 2904 (sp^3 C-H), 1433 (aromatic C=C), 1391 (aromatic C=C), 1246 (P=O), 1018 (C-O), 950 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{11}H_{17}O_3PS+Na^+$ = 283.0534, found 283.0533 *m/z*.



Synthesis of allylic phosphonate (*E*)-18r: Following **GP2**, the allyl bromide (*E*)-**86r** (127 mg, 0.50 mmol) yields alkene substrate (*E*)-**18r** (127 mg, 82%) as a viscous oil: TLC analysis (ethyl acetate/hexanes 4:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.75 (1H, m, aryl), 7.70-7.68 (1H, m, aryl), 7.34-7.27 (2H, m, aryl), 7.13 (1H, s, g), 6.78 (1H, dd, *J* = 15.5, 5.5 Hz, e), 6.15-6.05 (1H, m, e), 4.22-4.09 (4H, m, b), 2.79 (2H, ddd, *J* = 22, 7.5, 1.2 Hz, c), 1.35 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142 (d, $^{4}J_{C\text{-}P}$ = 4.5 Hz, f), 140.13 (d, $^{6}J_{C\text{-}P}$ = 1.2 Hz, h), 138.99 (m), 128.65 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 124.88 (aryl), 124.62 (aryl), 123.62 (aryl), 122.73 (d, $^{5}J_{C\text{-}P}$ = 3.5 Hz, g), 122.36 (aryl), 121.45 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 62.37 (d, $^{2}J_{C\text{-}P}$ = 6.7 Hz, b), 31.27 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 16.67 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.06 ppm; IR (neat) 2980 (sp^2 C-H), 2904 (sp^3 C-H), 1245 (P=O), 1017 (C-O), 951 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{19}O_3PS+Na^+$ = 333.0690, found 333.0693 *m/z*.

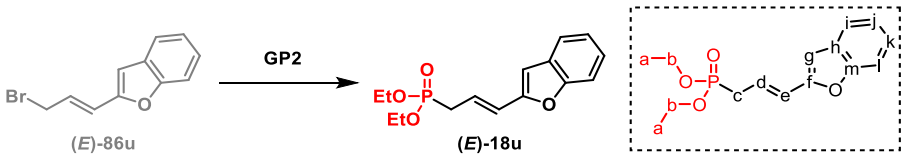


Synthesis of allylic phosphonate (*E*)-18s: Following **GP3**, the allyl carbonate (*E*)-**86s** (785 mg, 4.00 mmol) yields alkene substrate (*E*)-**18s** (288 mg, 30%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, br s, g), 7.34 (1H, dd, *J* = 1.5, 1.0 Hz, h), 6.52 (1H, d, *J* = 1.7 Hz, h), 6.38 (1Hh, dd, *J* = 15.75, 5.0 Hz, e), 5.93-5.83 (1H, m, d), 4.18-4.05 (4H, m, b), 2.71 (2H, ddd, *J* = 22.0, 7.50, 1.25 Hz, c), 1.32 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.66 (i), 140.32 (d, $^5J_{C\text{-}P}$ = 3.5 Hz, g), 124.55 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 123.98 (d, $^4J_{C\text{-}P}$ = 3.5 Hz, f), 118.40 (d, $^2J_{C\text{-}P}$ = 12 Hz, d), 107.64 (h), 62.18 (d, $^2J_{C\text{-}P}$ = 6.7 Hz, b), 31.08 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 16.62 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.94 ppm; IR (neat) 2981 (C-H), 1507 (aromatic C=C), 1443 (aromatic C=C), 1391 (aromatic C=C), 1246 (P=O), 1161, 1017 (C-O), 955 (P-O), 870, 773 cm^{-1}; HRMS (ESI) calculated for $C_{11}H_{17}O_4P+Na^+$ = 267.0757, found 267.0757 *m/z*.

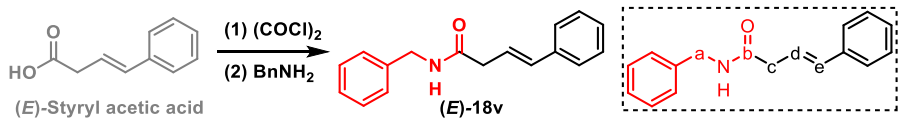


Synthesis of allylic phosphonate (*E*)-18t: Following **GP3**, the allyl carbonate (*E*)-**86t** (210 mg, 1.00 mmol) yields alkene substrate (*E*)-**18t** (119 mg, 46%) as a buff colored oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (1H, dd, *J* = 15.75, 5.5 Hz, e), 6.09 (1H, dd, *J* = 2.5, 2.0 Hz, g), 6.07-5.96 (1H, m, d), 5.96-5.95 (1H, m, h), 4.19-4.09 (4H, m, b), 2.72 (2H, ddd, *J* = 22.5, 7.5, 1.2 Hz, c), 2.31 (3H, s, j), 1.34 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.10 (i), 150.95 (d, $^4J_{C\text{-}P}$ = 4.5 Hz, f), 123.24 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 115.78 (d, $^2J_{C\text{-}P}$ = 12.5 Hz, d), 108.85 (d, $^5J_{C\text{-}P}$ = 3.0 Hz, g), 107.38 (h), 62.17 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b), 30.98 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 16.62 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a), 13.79 (j) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.78 ppm; IR (neat) 2982

(sp^2 C-H), 2906 (sp^3 C-H), 1592 (C=C), 1534, 1443 (aromatic C=C), 1391 (aromatic C=C), 1248 (P=O), 1017 (C-O), 954 (P-O), 774 cm^{-1}; HRMS (ESI) calculated for $C_{12}H_{19}O_4P+Na^+$ = 281.0919, found 281.0922 *m/z*.

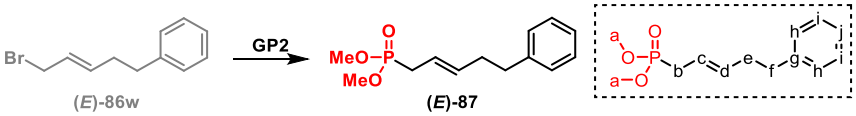


Synthesis of allylic phosphonate (*E*)-18u: Following **GP2**, the allyl bromide (*E*)-**86u** (118 mg, 0.50 mmol) yields alkene substrate (*E*)-**18u** (125 mg, 85%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 4:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 7.5 Hz, i or l), 7.44 (1H, d, *J* = 7.5 Hz, i or l), 7.29-7.18 (2H, m, j+k), 6.56 (1H, br s, g), 6.53-6.37 (2H, m, d+e), 4.23-4.10 (4H, m, b), 2.82 (2H, dd, *J* = 22, 7.5 Hz, c), 1.36 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.93 (m), 154.21 (d, $^4J_{C\text{-}P}$ = 4.5 Hz, f), 129.00 (d, $^6J_{C\text{-}P}$ = 1.35 Hz, h), 124.72 (j or k), 123.29 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 122.99 (j or k), 121.44 (d, $^2J_{C\text{-}P}$ = 12 Hz, d), 121.06 (i or l), 111.12 (i or l), 104.45 (d, $^5J_{C\text{-}P}$ = 3.5 Hz, g), 62.36 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b), 31.29 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 16.67 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.05 ppm; IR (neat) 2980 (sp^2 C-H), 2904 (sp^3 C-H), 1451 (aromatic C=C), 1391 (aromatic C=C), 1250 (P=O), 1018 (C-O), 944 (P-O), 748 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{19}O_4P+Na^+$ = 317.0919, found 317.0920 *m/z*.



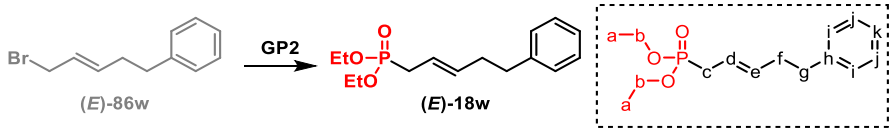
Synthesis of benzylamide substrate (*E*)-18v: To a solution of styryl acetic acid (486 mg, 3.00 mmol, 1.00 eq) in dry dichloromethane (15 mL) at 0 °C is added a drop of dry DMF. To the resultant mixture is added oxalyl chloride (0.38 mL, 4.50 mmol, 1.50 eq) drop wise

and the resultant mixture is stirred at room temperature for *ca.* 2 hours. Following this, the reaction mixture is subjected to rotary evaporation to get rid of unreacted oxalyl chloride. The crude mass is redissolved in dry dichloromethane (15 mL) and benzylamine (0.66 mL, 6.00 mmol, 2.00 eq) is added dropwise and the resultant mixture is stirred for *ca.* 2 hours. The mixture is concentrated via rotary evaporation and flash chromatography over silica gel (ethyl-acetate/hexanes/dichloromethane 40:50:10) affords the benzylamide product (*E*)-**17** (580 mg, 77%) as yellowish-white flaky solid: Melting point = 122-124 ºC; TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.25 (10H, m, aryl), 6.54 (1H, d, *J* = 16 Hz, e), 6.33 (1H, dt, *J* = 15.5, 7.5 Hz, d), 6.17 (1H, br s, NH), 4.46 (2H, d, *J* = 6.0 Hz, a), 3.21 (2H, dd, *J* = 7.5, 1.1 Hz, c) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.75 (b), 138.35 (aryl), 136.71 (aryl), 134.79 (e), 128.86 (aryl), 128.77 (aryl), 127.92 (aryl), 127.67 (aryl), 126.47 (aryl), 122.48 (d), 43.82 (a), 40.95 (c) ppm; IR (neat) 3235 (N-H), 3035 (C-H), 2160 (C=N), 1630 (C=O), 1539 cm^{-1}.

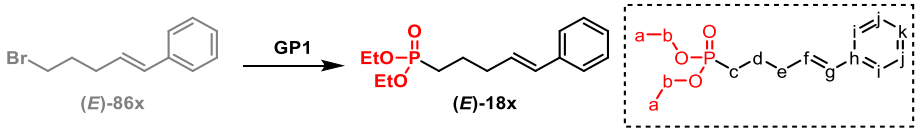


Preparation of disubstituted allylic phosphonate (*E*)-87: Following **GP2** (with dimethyl phosphite) the allyl bromide (*E*)-**86w** (225 mg, 1.00 mmol) yields dimethyl phosphonate alkene substrate (*E*)-**87** (211 mg, 83%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.17 (5H, m, aryl), 5.76-5.64 (1H, m, e), 5.50-5.41 (1H, m, d), 3.73 (6H, d, $^3J_{P\text{-}H}$ = 11 Hz, a), 2.71 (2H, t, *J* = 7.75 Hz, f), 2.58 (2H, dd, $^2J_{C\text{-}P}$ = 22 Hz, $^3J_{H\text{-}H}$ = 7.5 Hz, b), 2.42-2.36 (2H, m, e) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.76 (g), 135.58 (d, $^3J_{C\text{-}P}$ = 15 Hz, c), 128.61 (h or i), 128.49 (h or i), 126.03 (j), 119.03 (d, $^2J_{C\text{-}P}$ = 11 Hz, c), 52.83 (d, $^2J_{C\text{-}P}$ = 6.8 Hz, a), 35.69 (d, $^5J_{C\text{-}P}$ = 3.5

Hz, f), 34.43 (d, $^{4}J_{C\text{-}P}$ = 2.0 Hz, e), 29.64 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, b) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.27 ppm; IR (neat) 2951 (sp^2 C-H), 2850 (sp^3 C-H), 1603 (C=C), 1496 (aromatic C=C), 1453 (aromatic C=C), 1400 (aromatic C=C), 1251 (P=O), 1022 (C-O), 968 (P-O), 850, 805, 747, 698 cm^{-1}.

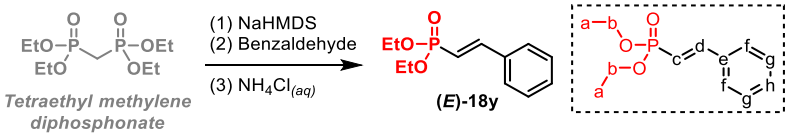


Preparation of disubstituted allylic phosphonate (*E*)-18w: Following **GP2**, the allyl bromide (*E*)-**86w** (225 mg, 1.00 mmol) yields alkene substrate (*E*)-**18w** (217 mg, 77%) as a colorless oil: TLC analysis (ethyl acetate/hexanes) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.18 (5H, m, aryl), 5.71-5.63 (1H, m, e), 5.51-5.42 (1H, m, d), 4.15-4.05 (4H, m, b), 2.71 (2H, t, *J* = 7.8 Hz, g), 2.56 (2H, dd, *J* = 21.5, 7.5 Hz, c), 2.42-2.37 (2H, m, f), 1.32 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.83 (h), 135.29 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 128.59 (i or j), 128.49 (i or j), 126.03 (k), 119.43 (d, $^{2}J_{C\text{-}P}$ = 11 Hz, d), 62.02 (d, $^{2}J_{C\text{-}P}$ = 7 Hz, b), 35.76 (d, $^{5}J_{C\text{-}P}$ = 3.5 Hz, g), 34.49 (d, $^{4}J_{C\text{-}P}$ = 2 Hz, f), 30.64 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 16.64 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.82 ppm; IR (neat) 2981 (sp^2 C-H), 2906 (sp^3 C-H), 1603 (C=C), 1496 (aromatic C=C), 1454 (aromatic C=C), 1391 (aromatic C=C), 1249 (P=O), 1021 (C-O), 957 (P-O), 698 cm^{-1}.



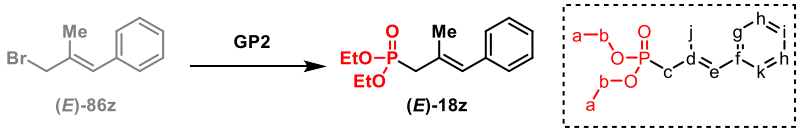
Preparation of disubstituted phosphonate (*E*)-18x: Following **GP1**, the allyl bromide (*E*)-**86x** (225 mg, 1.00 mmol) yields alkene substrate (*E*)-**18x** (184 mg, 65%) as a colorless oil: TLC analysis (ethyl acetate/hexanes) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-

7.20 (5H, m, aryl), 6.42 (1H, d, J = 15.8 Hz, g), 6.18 (1H, dt, J = 15.8, 7.0 Hz, f), 4.18-4.05 (4H, m, b), 2.35-2.30 (2H, m, e), 1.89-1.74 (4H, m, c+d), 1.34 (6H, t, J = 7 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.64 (h), 131.26 (g), 129.34 (f), 128.68 (i or j), 127.23 (k), 126.16 (i or j), 61.61 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b), 33.79 (d, $^{3}J_{C\text{-}P}$ = 17 Hz, e), 25.29 (d, $^{1}J_{C\text{-}P}$ = 141 Hz, c), 22.35 (d, $^{2}J_{C\text{-}P}$ = 5 Hz, d), 16.67 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.21 ppm; IR (neat) 3025 (sp^2 C-H), 2980 (sp^3 C-H), 1701 (C=C), 1493 (aromatic C=C), 1448 (aromatic C=C), 1390 (aromatic C=C), 1236 (P=O), 1022 (C-O), 955 (P-O), 693 cm^{-1}.

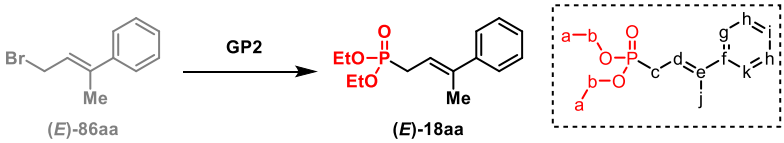


Synthesis of vinyl phosphonate substrate (*E*)-18y: To a solution of tetraethyl-methylene-diphosphonate (288 mg, 1.00 mmol, 1.00 eq) in dry THF (10 mL) at 0 °C is added NaHMDS (2M solution in THF; 0.6 mL, 1.2 mmol, 1.2 eq) dropwise, and the resultant solution is stirred for 10 minutes. To the resultant mixture is added benzaldehyde (0.11 mL, 1.10 mmol, 1.10 eq) and the resultant mixture is stirred at room temperature for 3 hours. Following this, a saturated aqueous solution of NH_4Cl (10 mL) is added to the reaction mixture and the layers separated. The aqueous layer is extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Flash chromatography over silica gel (ethyl acetate) affords the desired vinyl phosphonate (*E*)-**18y** (202 mg, 84%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.37 (6H, m, d+f+g+h), 6.27 (1H, dd, J = 17.5 Hz, c), 4.21-4.07 (4H, m, b), 1.36 (6H, t, J = 7 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.92 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, d), 135.02 (d, $^{3}J_{C\text{-}P}$ = 23

Hz, e), 130.40 (h), 129.01 (f or g), 127.86 (f or g), 114.12 (d, $^{1}J_{C\text{-}P}$ = 191 Hz, c), 62.04 (d, $^{2}J_{C\text{-}P}$ = 5.5 Hz, b), 16.57 (d, $^{3}J_{C\text{-}P}$ = 6.5 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.50 ppm; IR (neat) 2981 (C-H), 1615 (C=C), 1449 (aromatic C=C), 1391 (aromatic C=C), 1242 (P=O), 1018 (C-O), 954 (P-O), 740 cm^{-1}.

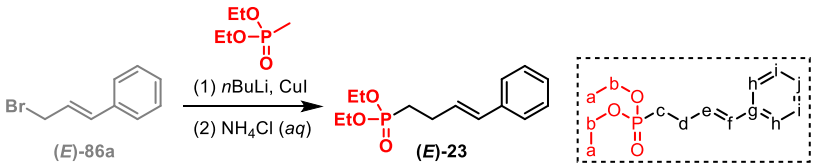


Preparation of trisubstituted allylic phosphonate (*E*)-18z: Following **GP2**, the allyl bromide (*E*)-**86z** (211 mg, 1.00 mmol) yields alkene substrate (*E*)-**18z** (228 mg, 85%) as a colorless oil: TLC analysis (ethyl acetate/hexanes) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.21 (5H, m, aryl), 6.43 (1H, d, *J* = 5.7 Hz, e), 4.21-4.07 (4H, m, b), 2.75 (2H, d, $^{2}J_{P\text{-}H}$ = 22.5 Hz, c), 2.03 (3H, d, *J* = 3.75 Hz, j), 1.34 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.83 (d, $^{4}J_{C\text{-}P}$ = 3.9 Hz, f), 129.79 (d, $^{3}J_{C\text{-}P}$ = 13 Hz, e), 129.52 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 128.96 (d, $^{6}J_{C\text{-}P}$ = 3 Hz, g), 128.27 (h), 126.59 (i), 62.11 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b), 38.19 (d, $^{1}J_{C\text{-}P}$ = 137 Hz, c), 19.31 (d, $^{3}J_{C\text{-}P}$ = 2.75 Hz, j), 16.66 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.10 ppm; IR (neat) 2981 (C-H), 1599 (C=C), 1444 (aromatic C=C), 1391 (aromatic C=C), 1247 (P=O), 1019 (C-O), 955 (P-O) cm^{-1}.

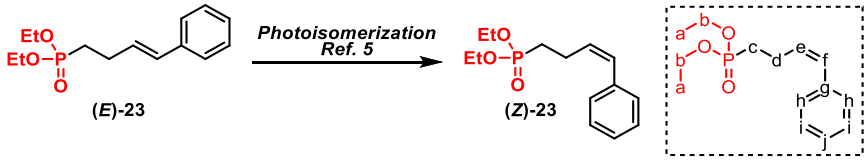


Preparation of trisubstituted allylic phosphonate (*E*)-18aa: Following **GP2**, the allyl bromide (*E*)-**86aa** (211 mg, 1.00 mmol) yields alkene substrate (*E*)-**18aa** (209 mg, 78%) as a colorless oil: TLC analysis (ethyl acetate/hexanes) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.24 (5H, m, aryl), 5.83-5.76 (1H, m, d), 4.18-4.09 (4H, m, b), 2.79 (2H,

ddd, J = 22.5, 8.0, 0.5 Hz, c), 2.09 (3H, dt, J = 4.0, 0.6 Hz, j), 1.34 (6H, t, J = 7 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.28 (d, $^{4}J_{C\text{-}P}$ = 3.6 Hz, f), 139.45 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 128.41 (h), 127.29 (i), 125.95 (d, $^{5}J_{C\text{-}P}$ = 2.25 Hz, g), 116.36 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 62.12 (d, $^{2}J_{C\text{-}P}$ = 7 Hz, b), 27.57 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 16.67 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a), 16.35 (d, $^{4}J_{C\text{-}P}$ = 2.5 Hz, j) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.65 ppm; IR (neat) 2980 (C-H), 1600 (C=C), 1494 (aromatic C=C), 1444 (aromatic C=C), 1390 (aromatic C=C), 1247 (P=O), 1019 (C-O), 955 (P-O), 757, 695 cm^{-1}.

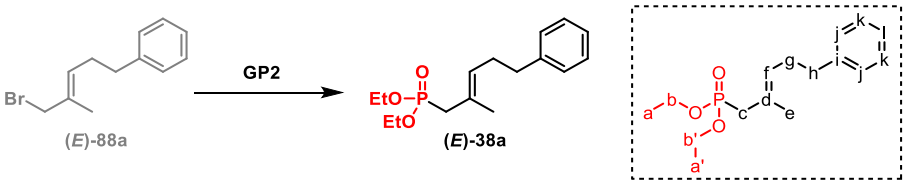


Preparation of disubstituted phosphonate (*E*)-23: This transformation is carried out via reaction between allyl bromides and lithiated diethyl methylphosphonate. The allyl bromide (*E*)-**86a** (197 mg, 1.00 mmol) yields alkene substrate (*E*)-**23** (190 mg, 71%) as a colorless oil: TLC analysis (ethyl acetate/hexanes) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.19 (5H, m, aryl), 6.44 (1H, d, J = 15.5 Hz, f), 6.23 (1H, dt, J = 15.5, 6.5 Hz, e), 4.19-4.06 (4H, m, b), 2.57-2.48 (d), 1.96-1.87 (2H, m, c), 1.34 (6H, t, J = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.43 (g), 130.79 (f), 129.18 (d, $^{3}J_{C\text{-}P}$ = 17 Hz, e), 128.71 (h or i), 127.38 (j), 126.23 (h or i), 61.72 (d, $^{2}J_{C\text{-}P}$ = 6 Hz, b), 26.18 (d, $^{2}J_{C\text{-}P}$ = 4.5 Hz, d), 25.79 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 16.68 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.19 ppm; IR (neat) 3025 (sp^2 C-H), 2980 (sp^3 C-H), 1597 (C=C), 1495 (aromatic C=C), 1442 (aromatic C=C), 1390 (aromatic C=C), 1240 (P=O), 1023 (C-O), 956 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{21}O_3P$+Na^+ = 291.1126, found 291.1129 *m/z*.



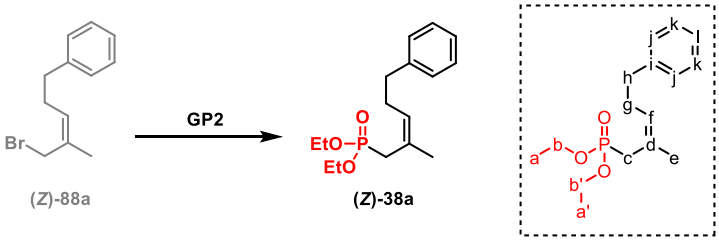
Synthesis of allylic phosphonate (*Z*)-23: Photoisomerization of the allylic phosphonate (*E*)-**23** (200 mg, 0.75 mmol; Ref. **5**) affords the diastereomeric (*Z*)-**23** (170 mg, 84%; Z:E ratio = 4:1) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (5H, m, aryl), 6.48 (1H, d, *J* = 12 Hz, f), 5.68 (1H, dt, *J* = 12, 7.0 Hz, e), 4.18-4.06 (4H, m, b), 2.68-2.62 (2H, m, d), 1.92-1.86 (2H, m, c), 1.32 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.22 (g), 131.12 (d, $^3J_{C\text{-}P}$ = 17 Hz, e), 130.11 (f), 128.89 (h or i), 128.45 (h or i), 127.03 (j), 61.76 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b), 26.21 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 21.91 (d, $^2J_{C\text{-}P}$ = 4.8 Hz, d), 16.65 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.05 ppm; IR (neat) 3026 (sp^2 C-H), 2978 (sp^3 C-H), 1597 (C=C), 1496 (aromatic C=C), 1440 (aromatic C=C), 1391 (aromatic C=C), 1237 (P=O), 1023 (C-O), 958 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{21}O_3P$+Na^+ = 291.1126, found 291.1127 *m/z*.

Synthesis of trisubstituted substrates.

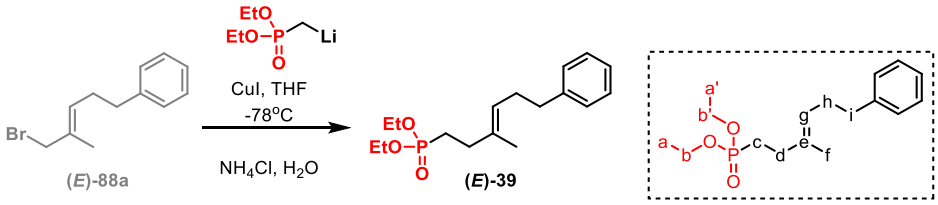


Synthesis of phosphonate functionalized alkene (*E*)-38a: Using **GP1**, allyl bromide (*E*)-**88a** (2.05 g, 8.57 mmol, 1.10 eq) yields substrate (*E*)-**38a** (1.65 g, 72%) as a clear, colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 3:2) R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.16 (5H, m, aryl), 5.37 (1H, dd, *J* = 6.6, 6.3 Hz, f), 4.07 (4H, doublet of quartets, *J*

= 7.5, 7.2 Hz, b+b'), 2.67 (2H, t, *J* = 7.5 Hz, h), 2.54 (2H, d, *J* = 21.6 Hz, c), 2.41-2.32 (2H, m, g), 1.74 (3H, d, 3 Hz, e), 1.30 (6H, t, *J* = 7.3 Hz a+a') ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.99 (i), 129.11 (d, $^{3}J_{C\text{-}P}$ = 12.8 Hz, f), 128.48 (aryl), 128.35 (aryl), 126.50 (d, $^{2}J_{C\text{-}P}$ = 11.3 Hz, d), 125.86 (aryl), 61.76 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz, b+b'), 36.88 (d, $^{1}J_{C\text{-}P}$ = 136.5 Hz, c), 35.74 (d, $^{5}J_{C\text{-}P}$ = 3.8 Hz, h), 30.17 (d, $^{4}J_{C\text{-}P}$ = 3 Hz, g), 17.40 (d, $^{3}J_{C\text{-}P}$ = 3 Hz, e), 16.53 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.89 ppm; IR (neat) 2980 (aromatic C-H), 2909 (aliphatic C-H), 1448.27 (C=C), 1245 (P=O) cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{25}O_3P$ 296.1541, found 296.1537 *m/z*.

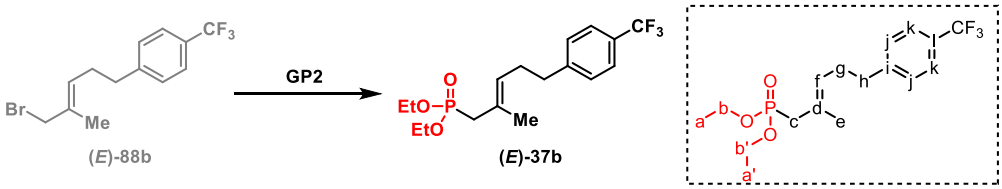


Synthesis of phosphonate functionalized alkene (*Z*)-38a: Using **GP2**, allyl bromide (*Z*)-**88a** (240 mg, 1.00 mmol) yielded (*Z*)-**38a** (174 mg, 76%) as a colorless viscous oil; TLC analysis (ethyl-acetate/hexanes 3:2) R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (2H, m, aryl), 7.19-7.16 (3H, m, aryl), 5.38 (1H, dd, *J* = 6.6, 13.4 Hz, f), 4.12-4.05 (4H, m, b+b'), 2.66 (2H, t, *J* = 7.8 Hz, h), 2.53 (2H, d, *J* = 22.8 Hz, c), 2.39-2.32 (2H, m, g), 1.85 (3H, q, *J* = 3.2, 1.2 Hz, e), 1.30 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.08 (aryl), 128.69 (aryl), 128.54 (aryl), 128.40 (aryl), 126.25 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 61.84 (d, $^{2}J_{C\text{-}P}$ = 7 Hz, b+b'), 35.80 (d, $^{5}J_{C\text{-}P}$ = 3 Hz, h), 30.39 (d, $^{1}J_{C\text{-}P}$ = 137 Hz, c), 30.37 (d, $^{4}J_{C\text{-}P}$ = 3 Hz, g), 24.93 (d, $^{3}J_{C\text{-}P}$ = 2 Hz, e), 16.60 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.60 ppm; IR (neat) 2978 (aromatic C-H), 2905 (aliphatic C-H), 1447 (C=C), 1247.90 (P=O) cm^{-1}.

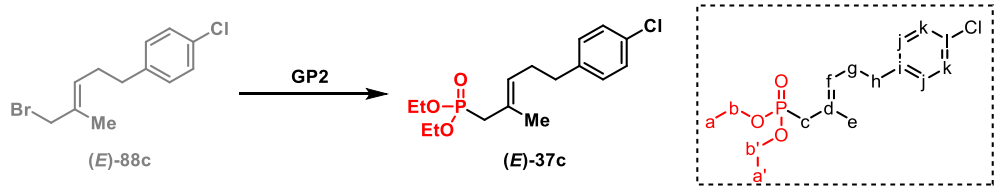


Synthesis of homologous phosphonate functionalized alkene substrate (*E*)-39: A solution of diethyl methylphosphonate (0.29 mL, 2.0 mmol) in THF (20 mL) is cooled to –78° C using a dry ice-acetone bath and *n*BuLi (1.3 mL; 1.6 M solution in hexanes, 2.1 eq) was added dropwise. The resultant mixture was stirred for 1 hour and then the mixture was warmed to –40° C in a dry ice-acetonitrile bath. Copper iodide (400 mg, 2.10 mmol, 1.05 eq) is added to the mixture and the resultant mixture is stirred at –40° C for 1 hour. The mixture is re-cooled to –78°C and a solution of allyl bromide **88a** (526 mg, 2.20 mmol, 1.10 eq) in THF (5 mL) added dropwise. The mixture is allowed to warm up to room temperature overnight and stirred for a total of 9 hours. Saturated NH_4Cl (aq) is added and the mixture extracted with 1:1 ethyl acetate/hexanes (3 x 20 mL). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated in vacuum. Flash chromatography on silica gel (ethyl acetate/hexanes 1:1) yielded the desired product as a colorless oil: TLC analysis (ethyl-acetate/hexanes 3:2) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.15 (5H, m, aryl), 5.23 (1H, t, *J* = 7.1 Hz, g), 4.14-4.04 (4H, m, b+b'), 2.63 (2H, t, *J* = 7.65 Hz, i), 2.33-2.20 (4H, m, d+h), 1.86-1.67 (2H, m, c), 1.54 (3H, s, f), 1.32 (6H, t, *J* = 7.1 Hz, a+a') ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.05 (aryl), 134.55 (d, $^3J_{C-P}$ = 18 Hz, e), 128.44 (aryl), 128.22 (aryl), 125.73 (aryl), 124.13 (g), 61.45 (d, $^2J_{C-P}$ = 6.75 Hz, b+b'), 35.89 (i), 31.97 (d, $^2J_{C-P}$ = 4.5 Hz, d), 29.86 (h), 16.48 (d, $^3J_{C-P}$ = 6 Hz, a+a'), 15.70 (f) ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 32.17 ppm; IR (neat) 2979 (aromatic C-H),

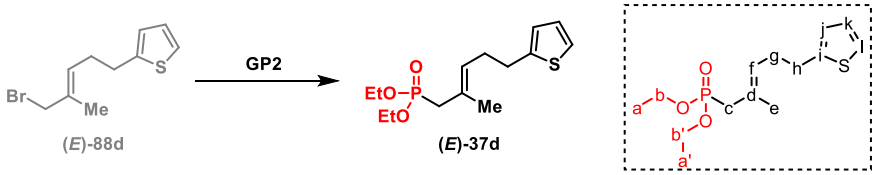
2860 (aliphatic C-H), 1603 (C=C), 1447, 1390, 1244 (P=O), 1025 (C-O), 954 (P-O), 698 cm^{-1}.



Synthesis of phosphonate functionalized alkene (*E*)-37b: Using **GP2**, the allyl bromide (*E*)-**88b** (307 mg, 1.00 mmol) yields substrate (*E*)-**37b** (302 mg, 83%) as a colorless, viscous oil: TLC analysis (ethyl-acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-1.51 (2H, m, k), 7.32-7.28 (2H, m, j), 5.36-5.33 (1H, m, f), 4.12-4.02 (4H, m, b+b'), 2.75-2.70 (2H, m, h), 2.53 (2H, d, *J* = 21.6, c), 2.39-2.37 (2H, m, g), 1.71 (3H, s, e), 1.33-1.28 (6H, m, a+a') ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.98 (aryl), 128.78 (aryl), 128.38 (aryl or vinyl), 128.20 (aryl or vinyl), 127.15 (aryl or vinyl), 127.00 (aryl or vinyl), 125.18 (aryl or vinyl), 125.13 (aryl or vinyl), 61.69 (d, $^{2}J_{C\text{-}P}$ = 6.75 Hz, b+b'), 36.74 (d, $^{1}J_{C\text{-}P}$ = 137.25 Hz, c), 35.44 (d, $^{5}J_{C\text{-}P}$ = 3.75 Hz, h), 29.69 (g), 17.35 (e), 16.41 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.72 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.33 ppm; IR (neat) 2983.20 (aromatic C-H), 2906.20 (aliphatic C-H), 1617.93 (C=C), 1443.92, 1323.55 (C-F), 1246.49 (P=O), 1161.18, 1119.47, 1054.30 (C-O), 1018.51 (C-O), 955.42, 834.85 cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{24}F_3O_3P$+Na^+ 387.1307, found 387.1311 *m/z*.

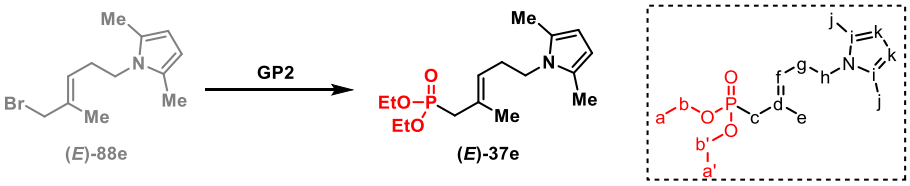


Synthesis of phosphonate functionalized alkene (*E*)-37c: Using **GP2**, allyl bromide (*E*)-**88c** (410 mg, 1.50 mmol) yields the alkene substrate (*E*)-**37c** (402 mg, 81%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 3:2) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.0 Hz, k), 7.13 (2H, d, *J* = 8.0 Hz, j), 5.39-5.31 (1H, m, f), 4.11-4.04 (4H, m, b+b'), 2.65 (2H, t, *J* = 7.6 Hz, h), 2.53 (2H, d, *J* = 22.0 Hz, c), 2.38-2.31 (2H, m, g), 1.72 (3H, d, *J* = 3.2 Hz, e), 1.31 (6H, t, *J* = 7.1 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.43 (aryl), 131.63 (aryl), 129.62 (aryl or vinyl), 128.74 (aryl or vinyl), 128.62 (aryl or vinyl), 128.52 (aryl or vinyl), 128.46 (aryl or vinyl), 128.40 (aryl or vinyl), 126.94 (d, $^{2}J_{C\text{-}P}$ = 11.0 Hz, d), 61.82 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b+b'), 36.89 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 35.08 (d, $^{5}J_{C\text{-}P}$ = 4 Hz, h), 30.03 (d, $^{4}J_{C\text{-}P}$ = 3 Hz, g), 17.48 (d, $^{3}J_{C\text{-}P}$ = 3 Hz, e), 16.57 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.80 ppm; IR (neat) 2981 (sp^2 C-H), 2862 (sp^3 C-H), 1492, 1443, 1390, 1246 (P=O), 1053 (C-O), 1024 (C-O), 955, 802 (C-Cl) cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{24}ClO_3P$+Na^+ 353.1044, found 353.1052 *m/z*.

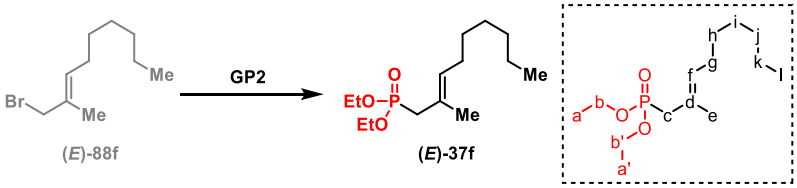


Synthesis of phosphonate functionalized alkene (*E*)-37d: Using **GP2** the allyl bromide (*E*)-**88d** (370 mg, 1.50 mmol) yields the alkene substrate (*E*)-**37d** (376 mg, 83%): TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.10 (1H, m, l), 6.92-6.90 (1H, m, k), 6.81-6.79 (1H, m, j), 5.40-5.33 (1H, m, f), 4.12-4.02 (4H, m, b+b'), 2.89 (2H, t, *J* = 7.5 Hz, h), 2.55 (2H, d, *J* = 21.9 Hz, c), 2.47-2.38 (2H, m, g), 1.77-1.76 (3H, m, e), 1.34 (6H, t, *J* = 4.5 Hz, a+a') ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.72 (i), 128.48 (d, $^{3}J_{C\text{-}P}$ = 12.8 Hz, f), 127.06 (d, $^{2}J_{C\text{-}P}$ = 11.3 Hz, d), 126.68 (k), 124.22 (j),

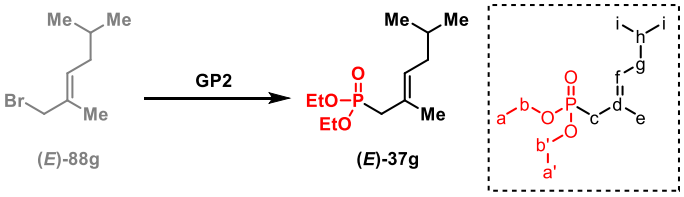
123.03 (l), 61.73 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz, b+b'), 36.81 (d, $^{1}J_{C\text{-}P}$ = 136.5 Hz, c), 30.36 (d, $^{4}J_{C\text{-}P}$ = 3 Hz, g), 29.71 (d, $^{5}J_{C\text{-}P}$ = 4.5 Hz, h), 17.43 (d, $^{3}J_{C\text{-}P}$ = 2.3 Hz, e), 16.46 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.76 ppm; IR (neat) 2979.64 (sp^2 C-H), 2906.49 (sp^3 C-H), 1441.35 (C=C), 1244.43 (P=O), 1023.49 (C=S), 693.98 (C-S) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_3PS$ = 302.1106, found 302.1111 *m/z*.



Synthesis of phosphonate functionalized alkene (*E*)-37e: Using **GP2**, allyl bromide (*E*)-**88e** (385 mg, 1.50 mmol) yields the alkene substrate (*E*)-**37e** (296 mg, 63%): TLC analysis (ethyl-acetate) R_f = 0.6; (Note: This molecule is sensitive to air, light and silica gel. For purification, the silica gel that was used is deactivated by packing with 3% trimethylamine in ethyl acetate and chromatography was performed quickly so that the exposure of this molecule to air/light and silica gel is greatly minimized) ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (2H, s, k), 5.37-5.31 (1H, m, f), 4.16-4.06 (4H, m, b+b'), 3.76-3.71 (2H, m, h), 2.57 (2H, d, *J* = 21.9 Hz, c), 2.40-2.31 (2H, m, g), 2.24 (6H, s, j), 1.77 (3H, d, *J* = 2.4 Hz, e), 1.33 (6H, t, *J* = 7.1 Hz, a+a') ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.85 (d, $^{2}J_{C\text{-}P}$ = 11.3 Hz, d), 127.22 (i), 125.23 (d, $^{3}J_{C\text{-}P}$ = 12.8 Hz, f), 105.17 (k), 61.79 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz, d), 42.95 (d, $^{5}J_{C\text{-}P}$ = 5.3 Hz, h), 36.86 (d, $^{1}J_{C\text{-}P}$ = 137.3 Hz, c), 29.96 (d, $^{4}J_{C\text{-}P}$ = 3 Hz, g), 17.29 (d, $^{3}J_{C\text{-}P}$ = 2.3 Hz, e), 16.47 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a'), 12.48 (j) ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.49 ppm; IR (neat) 2977.57 (sp^2 C-H), 2905.38 (sp^3 C-H), 1630 (C=C), 1407.55 (C=N), 1244.51 (P=O), 1088.81 (C-N) cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{28}NO_3P$ 313.1807, found 313.1804 *m/z*.

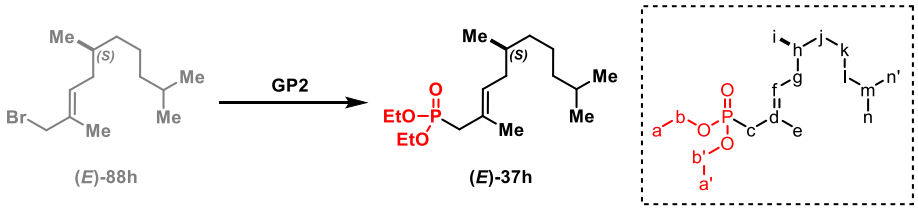


Synthesis of phosphonate functionalized alkene (*E*)-37f: Using **GP2**, the allyl bromide (*E*)-**88f** (329 mg, 1.50 mmol) yields substrate (*E*)-**37f** (336 mg, 81%) as a colorless oil: TLC analysis (EtOAc:hexanes 2:3) R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34-5.27 (1H, m, f), 4.11-4.04 (4H, m, b+b'), 2.52 (2H, d, *J* = 21.6 Hz, c), 2.02-1.99 (2H, m, g), 1.75 (3H, s, e), 1.31-1.26 (14H, m, a+a'+h+i+j+k), 0.88-0.85 (3H, m, l) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.50 (d, $^{3}J_{C\text{-}P}$ = 13 Hz, f), 125.54 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 61.82 (d, $^{2}J_{C\text{-}P}$ = 7 Hz, b+b'), 37.03 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 31.92 (j), 29.63 (d, $^{4}J_{C\text{-}P}$ = 4 Hz, g), 29.10 (i), 28.36 (d, $^{5}J_{C\text{-}P}$ = 2 Hz, h), 22.80 (k), 17.44 (d, $^{3}J_{C\text{-}P}$ = 3 Hz, e), 16.60 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a'), 14.24 (l) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.12 ppm; IR (neat) 2956 (sp^2 C-H), 2856 (sp^3 C-H), 1249 (P=O), 1025 (C-O), 955 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{29}O_3P+Na^+$ 299.1747, found 299.1751 *m/z*.

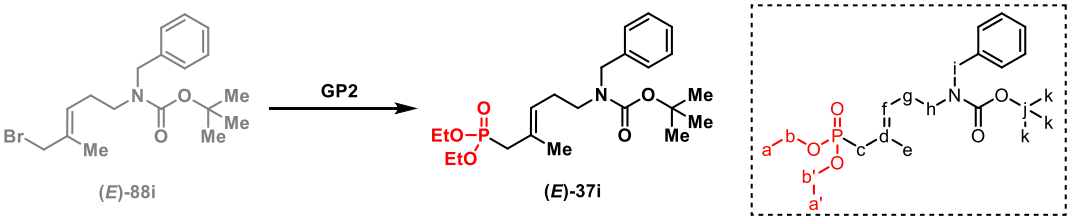


Synthesis of phosphonate functionalized alkene (*E*)-37g: Using **GP2**, the allyl bromide (*E*)-**88g** (230 mg, 1.50 mmol) yields substrate (*E*)-**37g** (323 mg, 83%) as a colorless oil: TLC analysis (EtOAc:hexanes 2:3) R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30-5.72 (1H, broad m, f), 4.09-3.99 (4H, m, b+b'), 2.51 (2H, d, *J* = 21.6 Hz, c), 1.90-1.84 (2H, m, g), 1.71 (3H, s, e), 1.62-1.53 (1H, m, h), 1.29-1.24 (6H, m, a+a'), 0.85 (6H, d, *J* = 6.0 Hz, i)

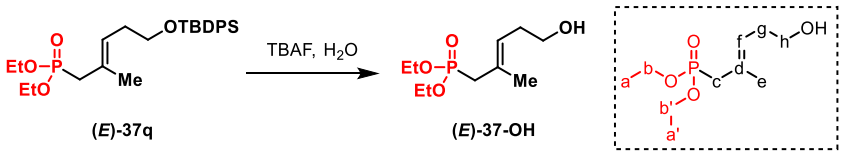
ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.11 (d, $^{3}J_{C\text{-}P}$ = 12.8 Hz, f), 125.95 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 61.63 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz, b+b'), 36.86 (d, $^{1}J_{C\text{-}P}$ = 136.5 Hz, c) 37.29 (d, $^{4}J_{C\text{-}P}$ = 2.3 Hz, g), 28.73 (d, $^{5}J_{C\text{-}P}$ = 3.8 Hz, h), 22.28 (i), 17.37 (d, $^{3}J_{C\text{-}P}$ = 2.3 Hz, e), 16.38 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.14 ppm; IR (neat) 2955.88 (aliphatic C-H), 1630 (C=C), 1246.78 (P=O) cm^{-1}; HRMS (ESI) calculated for $C_{12}H_{25}O_3P$ 248.1541, found 248.1541 *m/z*.



Synthesis of phosphonate functionalized alkene (*E*)-37h: Using **GP2**, the allyl bromide (*E*)-**88h** (393 mg, 1.50 mmol) yields the alkene substrate (*E*)-**37h** (408 mg, 85%): TLC analysis (1:1 EtOAc:Hexanes) R_f = 0.5; $[\alpha]_D^{20}$ = –2.9° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34-5.29 (1H, m, f), 4.12-4.05 (4H, m, b+b'), 2.55 (2H, d, *J* = 21.6 Hz, c), 2.04-1.97 (1H, m, g), 1.90-1.75 (1H, m, g), 1.75 (3H, s, e), 1.58-1.44 (2H, m, h+m), 1.34-1.00 (12H, m, a+a'+j+k+l), 0.87-0.85 (9H, overlapping doublets, i+n+n') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.07 (d, $^{3}J_{C\text{-}P}$ = 10.5 Hz, f), 126.01 (d, $^{2}J_{C\text{-}P}$ = 12.25 Hz, d), 61.63 (d, $^{2}J_{C\text{-}P}$ = 7 Hz, b+b'), 39.29, 36.96 (d, $^{1}J_{C\text{-}P}$ = 136.5 Hz, c), 36.91, 35.52, 33.54, 27.97, 24.89, 22.65, 19.55 (i), 17.45 (d, $^{3}J_{C\text{-}P}$ = 2 Hz, e), 16.47 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.11 ppm; IR (neat) 2953.39 (sp^2 C-H), 2866.96 (sp^3 C-H), 1630 (C=C), 1249.72 (P=O), 1025.58, 955.88 cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{35}O_3P$+Na^+ 341.2216, found 341.2227 *m/z*.

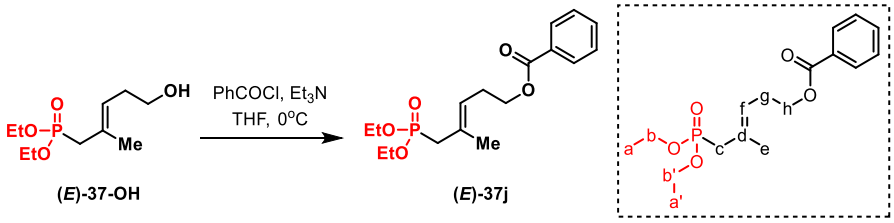


Synthesis of phosphonate functionalized alkene (*E*)-37i: Using **GP2**, the allyl bromide (*E*)-**88i** (368 mg, 1.00 mmol) yields the alkene substrate (*E*)-**37i** (335 mg, 78%): TLC analysis (EtOAc) R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$, 333K) δ 7.33-7.23 (5H, m, aryl), 5.29-5.24 (1H, m, f), 4.45 (2H, s, i), 4.12-4.05 (4H, m, b+b'), 3.19 (2H, t, *J* = 6.8 Hz, h), 2.52 (2H, d, *J* = 22.0 Hz, c), 2.28-2.25 (2H, m, g), 1.76 (3H, d, *J* = 2.8 Hz, e), 1.49 (9H, s, k), 1.31 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 333K) δ 155.78 (carbonyl C), 138.79 (aryl), 128.46 (aryl), 128.20 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 127.57 (aryl), 127.12 (aryl), 126.29 (d, $^{3}J_{C\text{-}P}$ = 13 Hz, f), 79.63 (j), 61.68 (d, $^{2}J_{C\text{-}P}$ = 6 Hz, b+b'), 50.86 (i), 46.47 (d, $^{5}J_{C\text{-}P}$ = 5 Hz, h), 37.15 (d, $^{1}J_{C\text{-}P}$ = 137 Hz, c), 28.53 (k), 27.46 (g), 17.29 (d, $^{3}J_{C\text{-}P}$ = 2 Hz, e), 16.40 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$, 333K) δ 27.39 ppm; IR (neat) 2976 (aromatic C-H), 2906 (aliphatic C-H), 1689 (carbamate C=O), 1244 (P=O), 1158 (C-O), 1024 (C-O), 957 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{22}H_{36}NO_5P+Na^+$ 448.2229, found 448.2239 *m/z*.



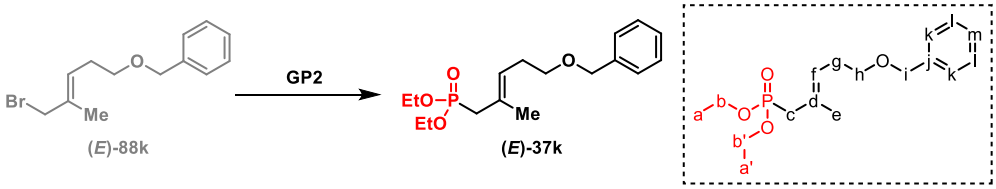
Synthesis of phosphonate containing unsaturated alcohol intermediate (*E*)-37-OH: Substrate (*E*)-**37q** (1.19 g, 2.50 mmol, 1.00 eq) is dissolved in 25 mL THF and the mixture is cooled to 0°C. TBAF (1.0 *M* in THF; 5 mL, 5.0 mmol, 2.0 eq) is added dropwise and the resultant mixture is stirred at room temperature overnight. Afterwards, the mixture is

concentrated under reduced pressure and flash chromatography on silica gel (ethyl-acetate/methanol 19:1) affords the desired unsaturated phosphonate alcohol intermediate (*E*)-**37-OH** (562 mg, 95%) as a clear, colorless viscous oil: TLC analysis (ethyl-acetate/methanol 10:1) R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23-5.16 (1H, m, f), 3.94-3.77 (5H, m, b+b'+OH), 3.40 (2H, t, *J* = 6.75 Hz, h), 2.37 (2H, d, *J* = 21.9 Hz, c), 2.14-2.10 (2H, m, g), 1.60 (3H, s, e), 1.13 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.44 (d, $^2J_{C\text{-}P}$ = 11.25 Hz, d), 126.39 (d, $^3J_{C\text{-}P}$ = 12.75 Hz, f), 61.75-61.40 (m, b+b'+h), 36.57 (d, $^1J_{C\text{-}P}$ = 136.5 Hz, c), 31.74 (d, $^2J_{C\text{-}P}$ = 3 Hz, g), 17.28 (d, $^3J_{C\text{-}P}$ = 2.25 Hz, e), 16.22 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.00 ppm. IR (neat) 3392 (O-H), 2981 (sp^2 C-H), 2907 (sp^3 C-H), 1229 (P=O), 1021 (C-O), 958 (P-O) cm^{-1}.



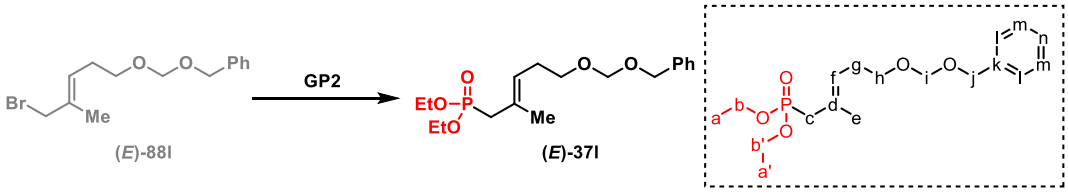
Synthesis of phosphonate functionalized alkene substrate (*E*)-37j: The alcohol (*E*)-**37-OH** (354 mg, 1.50 mmol) is dissolved in 15 mL THF and the reaction mixture is cooled to 0°C. Triethylamine (0.52 mL, 3.7 mmol, 2.5 eq) is added in one portion followed by benzoyl chloride (0.26 mL, 2.2 mmol, 1.5 eq) dropwise. The resultant mixture is warmed to room temperature and stirred for a total of 2 hours. Saturated $NaHCO_3$ solution is added and the mixture is extracted with ethyl-acetate (3 x 20 mL). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (ethyl-acetate) affords the desired substrate (*E*)-**37j** (388 mg, 76%) as a colorless oil: TLC analysis (ethyl-acetate) R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-8.02 (2H, m,

aryl), 7.57-7.41 (3H, m, aryl), 5.42-5.37 (1H, m, f), 4.32 (2H, t, *J* = 6.8 Hz, h), 4.11-4.03 (4H, m, b+b'), 2.58 (2H, d, *J* = 22.4 Hz, c), 2.55-2.49 (2H, m, g), 1.84 (3H, d, *J* = 2.8 Hz, e), 1.28 (6H, t, *J* = 7.1 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.68 (carbonyl), 132.99 (aryl), 130.41 (aryl), 130.41 (aryl), 129.64 (aryl), 129.20 (d, $^{2}J_{C\text{-}P}$ = 12 Hz, d), 128.43 (aryl), 124.83 (d, $^{3}J_{C\text{-}P}$ = 13 Hz, f), 64.28 (d, $^{5}J_{C\text{-}P}$ = 4 Hz, h), 61.90 (d, $^{2}J_{C\text{-}P}$ = 7.00 Hz, b+b'), 37.00 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 28.00 (d, $^{4}J_{C\text{-}P}$ = 2.00 Hz, g), 17.63 (d, $^{3}J_{C\text{-}P}$ = 3.00 Hz, e), 16.52 (d, $^{3}J_{C\text{-}P}$ = 6.00 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.44 ppm; IR (neat) 2982 (sp^2 C-H), 2905 (sp^3 C-H), 1716 (C=O), 1602 (C=C), 1269 (P=O), 1053 (C-O), 1023 (C-O), 956, 711, 583 cm^{-1}. HRMS (ESI) calculated for $C_{17}H_{25}O_5P+Na^+$ 363.1332, found 363.1339 *m/z*.

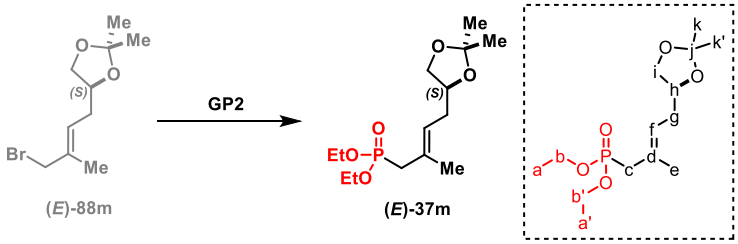


Synthesis of phosphonate functionalized alkene (*E*)-37k: Using **GP2**, allyl bromide (*E*)-**88k** (336 mg, 1.50 mmol) yields the alkene substrate (*E*)-**37k** (321 mg, 76%): TLC analysis (ethyl-acetate/hexanes 3:2) R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.22 (5H, m, aryl), 5.37-5.30 (1H, m, f), 4.49 (2H, s, i), 4.10-4.01 (4H, m, b+b'), 3.46 (2H, t, *J* = 6.9 Hz, h), 2.54 (2H, d, *J* = 21.9 Hz, c), 2.40-2.31 (2H, m, g), 1.78 (3H, d, *J* = 3 Hz, e), 1.27 (6H, t, *J* = 7.1 Hz, a+a') ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.43 (j), 128.32 (aryl), 127.75 (d, $^{2}J_{C\text{-}P}$ = 11.3 Hz, d), 127.58 (aryl), 127.50 (aryl), 125.96 (d, $^{3}J_{C\text{-}P}$ = 13.5 Hz, f), 72.87 (i), 69.66 (d, $^{5}J_{C\text{-}P}$ = 4.5 Hz, h), 61.73 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz, b+b'), 36.88 (d, $^{1}J_{C\text{-}P}$ = 136.5 Hz, c), 28.94 (d, $^{4}J_{C\text{-}P}$ = 2.3 Hz, g), 17.46 (d, $^{3}J_{C\text{-}P}$ = 2.3 Hz, e), 16.42 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.69 ppm; IR (neat) 2980.94 (C-H), 1453.82 (C=C),

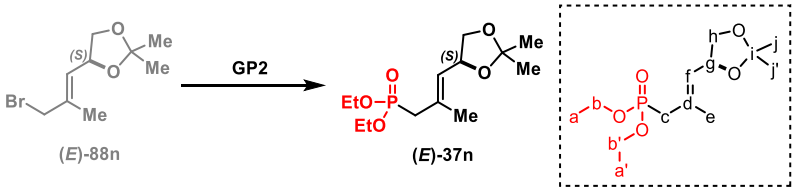
1245.73 (P=O), 1097.75 (C-O) cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{27}O_4P$: 326.1647, found 326.1631 *m/z*.



Synthesis of phosphonate functionalized alkene (*E*)-37l: Using **GP2,** the allyl bromide (*E*)-**88l** (450 mg, 1.50 mmol) yields the alkene substrate (*E*)-**37l** (413 mg, 77%): TLC analysis (ethyl-acetate) R_f = 0.6; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.32 (5H, m, aryl), 5.39-5.32 (1H, m, f), 4.77 (2H, s, j), 4.62 (2H, s, i), 4.18-4.00 (4H, m, b+b'), 3.62 (2H, t, *J* = 6.9 Hz, h), 2.57 (2H, d, *J* = 21.6 Hz, c), 2.42-2.33 (2H, m, g), 1.81 (3H, d, *J* = 2.7 Hz, e), 1.32 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.93 (k), 128.43 (aryl), 128.03 (d, $^2J_{C\text{-}P}$ = 11.25 Hz, d), 127.85 (aryl), 127.69 (aryl), 125.86 (d, $^3J_{C\text{-}P}$ = 13.5 Hz, f), 94.60 (i), 69.34 (j), 67.33 (d, $^5J_{C\text{-}P}$ = 4.5 Hz, h), 61.76 (d, $^2J_{C\text{-}P}$ = 6.75 Hz, b+b'), 36.92 (d, $^1J_{C\text{-}P}$ = 136.5 Hz, c), 28.89 (d, $^4J_{C\text{-}P}$ = 3 Hz, g), 17.50 (d, $^3J_{C\text{-}P}$ = 2.25 Hz, e), 16.46 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.71 ppm; IR (neat) 2978.88 (sp^2 C-H), 2903.19 (sp^3 C-H), 1246.33 (P=O), 1022.29 (C-O), 954.90 (C-O) cm^{-1}; HRMS (ESI) calculated for $C_{18}H_{29}O_5P$+Na^+ 379.1645, found 379.1651 *m/z*.

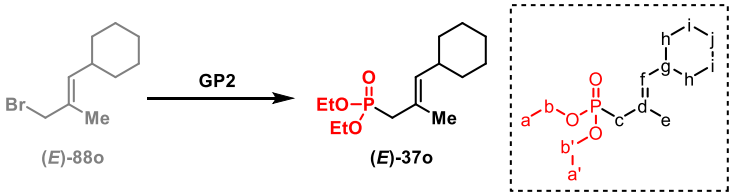


Synthesis of phosphonate functionalized alkene (*E*)-37m: Using **GP2**, allyl bromide (*E*)-**88m** (374 mg, 1.50 mmol) yields the alkene substrate (*E*)-**37m** (376 mg, 82%): TLC analysis (EtOAc) R_f = 0.4; $[\alpha]_D$ = +1.4° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34-5.29 (1H, m, f), 4.15-4.00 (6H, m, b+b'+h+i(1H)), 3.55 (1H, dd, *J* = 6.8, 6 Hz, i), 2.56 (2H, d, *J* = 21.6 Hz, c), 2.45-2.24 (2H, m, g), 1.80 (3H, d, *J* = 2.4 Hz), 1.42 (3H, s, k or k'), 1.35 (3H, s, k or k'), 1.31 (6H, t, *J* = 6.8 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.88 (d, $^2J_{C\text{-}P}$ = 11 Hz, d), 124.45 (d, $^3J_{C\text{-}P}$ = 13 Hz, f), 109.01 (j), 75.63 (d, $^5J_{C\text{-}P}$ = 4 Hz, h), 69.10 (i), 61.86 (d, $^2J_{C\text{-}P}$ = 7 Hz, b+b'), 37.06 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 32.61 (d, $^4J_{C\text{-}P}$ = 3 Hz, g), 27.00 (k or k'), 25.75 (k or k'), 17.74 (d, $^3J_{C\text{-}P}$ = 2 Hz, e), 16.56 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a'); ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.51 ppm; IR (neat) 2958.99 (sp^2 C-H), 2877.73 (sp^3 C-H), 1673.16 (C=C), 1233.36 (P=O), 1054.15 (C-O), 950.27 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{27}O_5P$ 306.1596, found 306.1600 *m/z*.

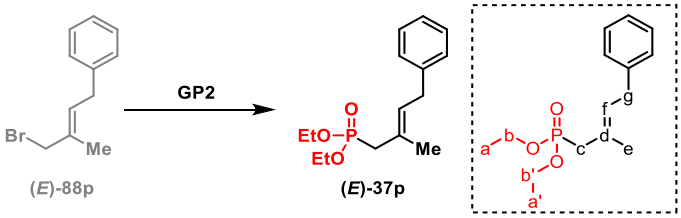


Synthesis of phosphonate functionalized alkene (*E*)-37n: Using **GP2**, allyl bromide (*E*)-**88n** (353 mg, 1.50 mmol) yields the alkene substrate (*E*)-**37n** (335 mg, 80%): TLC analysis (ethyl-acetate) R_f = 0.4; $[\alpha]_D$ = +2.7° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35-5.31 (1H, m, f), 4.80-4.74 (1H, m, g), 4.09-4.03 (5H, m, b+b' & h (1H)), 3.50 (1H, t, *J* = 8 Hz, h (1H)), 2.64-2.46 (2H, m, c), 1.85 (3H, m, e), 1.38 (3H, s, j or j'), 1.36 (3H, s, j or j'), 1.28 (6H, t, *J* = 7.2 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.30 (d, $^2J_{C\text{-}P}$ = 11 Hz, d), 127.59 (d, $^3J_{C\text{-}P}$ = 12 Hz, f), 109.07 (i), 72.79 (d, $^4J_{C\text{-}P}$ = 3 Hz, g), 69.31 (d, $^5J_{C\text{-}P}$ = 4 Hz, h), 61.98 (d, $^2J_{C\text{-}P}$ = 7 Hz, b+b'), 37.11 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 26.84 (j or j'), 26.00 (j

or j'), 18.04 (d, $^{3}J_{C\text{-}P}$ = 2 Hz, e), 16.54-16.45 (m, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.49 ppm; IR (neat) 2983.21 (sp^2 C-H), 2935.94 (sp^2 C-H), 1671.36 (C=C), 1245.26 (P=O), 1051.13 (C-O), 956.40 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{25}O_5P$ 292.1440, found 292.1454 *m/z*.

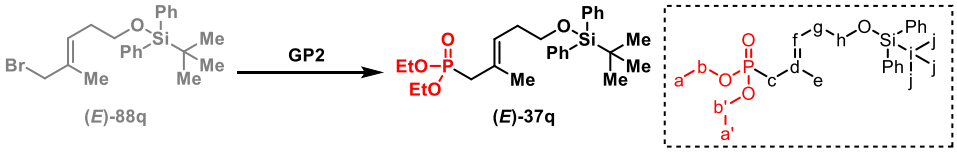


Synthesis of phosphonate functionalized alkene (*E*)-37o: Using **GP2**, allyl bromide (*E*)-**88o** (320 mg, 1.50 mmol) yields substrate (*E*)-**37o** (306 mg, 76%) as a colorless viscous oil: TLC analysis (ethyl-acetate:hexanes 1:1) R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14-5.09 (1H, br m, f), 4.11-4.01 (4H, m, b+b'), 2.50 (2H, d, *J* = 21.9 Hz, c), 2.22-2.14 (1H, m, g), 1.81-0.96 (19H, m, e+a+a'+h+i+j) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.24 (d, $^{3}J_{C\text{-}P}$ = 12.8 Hz, f), 123.80 (d, $^{2}J_{C\text{-}P}$ = 11.3 Hz, d), 61.73 (d, $^{2}J_{C\text{-}P}$ = 6.8 Hz, b+b'), 36.87 (d, $^{1}J_{C\text{-}P}$ = 135.8 Hz, f), 37.23 (d, $^{4}J_{C\text{-}P}$ = 2.3 Hz, g), 32.96 (d, $^{5}J_{C\text{-}P}$ = 4.5 Hz, h), 26.02 (j), 25.92 (i), 17.38 (d, $^{3}J_{C\text{-}P}$ = 2.3 Hz, e), 16.43 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.00 ppm; IR (neat) 2922 (C-H), 1625 (C=C), 1246.13 (P=O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{27}O_3P$ 274.1698, found 274.1691 *m/z*.



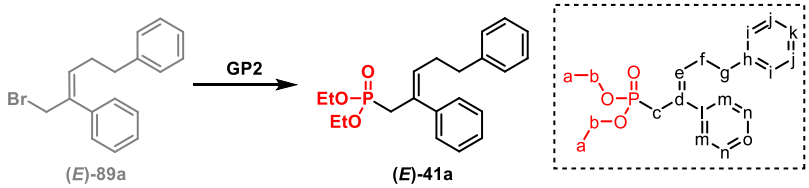
Synthesis of phosphonate functionalized alkene (*E*)-37p: Using **GP2**, allyl bromide (*E*)-**88p** (338 mg, 1.50 mmol) yields substrate (*E*)-**37p** (288 mg, 68%) as a colorless viscous

oil: TLC analysis (ethyl-acetate/hexanes 3:2) R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.18 (5H, m, aryl), 5.55-5.49 (1H, m, f), 4.12-4.03 (4H, m, *J* = 7.2 Hz, b+b'), 3.41 (2H, t, *J* = 6.0 Hz, g), 2.60 (2H, d, *J* = 21.9 Hz, c), 1.90 (3H, d, *J* = 3 Hz, e), 1.29 (6H, t, *J* = 7.1 Hz, a+a') ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.84 (d, $^5J_{C\text{-}P}$ = 3.8 Hz, h), 128.53 (aryl), 128.40 (aryl), 128.36 (aryl), 128.32 (aryl), 126.90 (d, $^2J_{C\text{-}P}$ = 11.3 Hz, d), 125.91 (aryl), 61.81 (d, $^2J_{C\text{-}P}$ = 6.8 Hz, b+b'), 36.89 (d, $^1J_{C\text{-}P}$ = 136.5 Hz, c), 34.43 (d, $^4J_{C\text{-}P}$ = 3 Hz, g), 17.44 (d, $^3J_{C\text{-}P}$ = 2.3 Hz, e), 16.41 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.71 ppm; IR (neat) 3026.05 (sp^2 C-H), 2980.86 (sp^3 C-H), 1624 (C=C), 1243.85 (P=O) cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{23}O_3P$ 282.1385, found 282.1373 *m/z*.

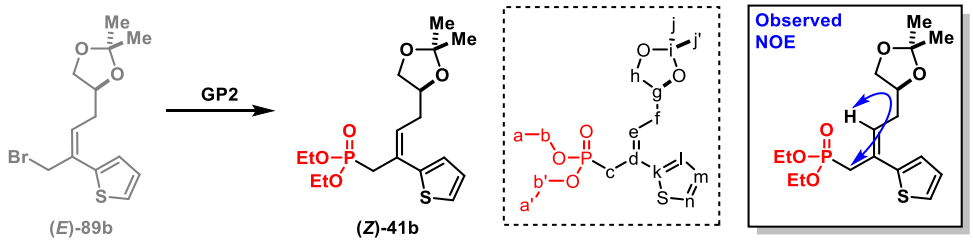


Synthesis of phosphonate functionalized alkene (*E*)-37q: Using **GP2**, allyl bromide (*E*)-**88q** (626 mg, 1.50 mmol) yielded the alkene substrate (*E*)-**37q** (592 mg, 83%): TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.67 (4H, m, aryl), 7.41-7.39 (6H, m, aryl), 5.35-5.33 (1H, m, f), 4.12-4.03 (4H, m, b+b'), 3.68 (2H, t, *J* = 6.9 Hz, h), 2.54 (2H, d, *J* = 21.6 Hz, c), 2.37-2.29 (2H, m, g), 1.74 (3H, br s, e), 1.29 (6H, t, *J* = 7.1 Hz, a+a'), 1.08 (9H, s, j) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.55 (aryl), 134.02 (d), 129.63 (aryl), 129.54 (aryl), 127.79 (aryl), 127.64 (aryl), 127.59 (aryl), 125.96 (d, $^3J_{C\text{-}P}$ = 13.5 Hz, f), 63.44 (d, $^5J_{C\text{-}P}$ = 5.25 Hz, h), 61.67 (d, $^2J_{C\text{-}P}$ = 6.75 Hz, b+b'), 37.03 (d, $^1J_{C\text{-}P}$ = 136.5 Hz, c), 31.85 (d, $^4J_{C\text{-}P}$ = 3 Hz, h), 26.87 (j), 19.17 (i), 17.35 (d, $^3J_{C\text{-}P}$ = 2.25 Hz, e), 16.40 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.18 ppm; IR

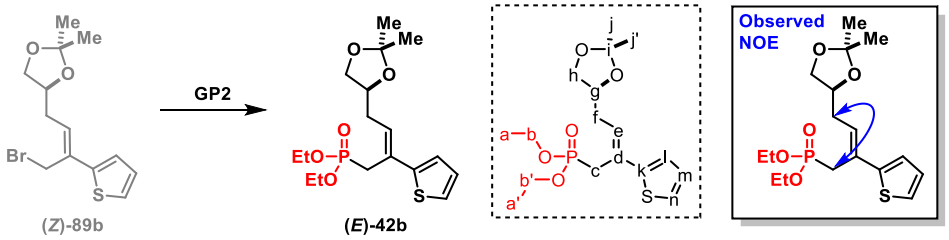
(neat) 3070.33 (sp^2 C-H), 2902.57 (sp^3 C-H), 1245.44 (P=O), 1054.07 (C-O), 1024.60 (C-O) cm^{-1}; HRMS (ESI) calculated for $C_{26}H_{39}O_4PSi+Na^+$ 497.2247, found 497.2272 *m/z*.



Synthesis of phosphonate functionalized alkene (*E*)-41a: Following **GP2**, allyl bromide (*E*)-**89a** (301 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*E*)-**41a** (319 mg, 89%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.11 (10H, m, aryl), 5.77 (1H, dd, *J* = 12.5, 7.0 Hz, e), 4.02-3.58 (4H, m, b), 2.92 (2H, d, $^2J_{P\text{-}H}$ = 21.5 Hz, c), 2.68 (2H, t, *J* = 7.5 Hz, g), 2.39-2.32 (2H, m, f), 1.18 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.76 (h), 140.34 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, d), 131.84 (d, $^3J_{C\text{-}P}$ = 12 Hz, e), 131.47 (d, $^3J_{C\text{-}P}$ = 10.5 Hz, l), 128.70 (aryl), 128.63 (aryl), 128.42 (aryl), 128.18 (aryl), 127.07 (aryl), 125.98 (aryl), 61.79 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b), 36.26 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 36.12 (d, $^5J_{C\text{-}P}$ = 4.00 Hz, g), 31.24 (d, $^4J_{C\text{-}P}$ = 2.0 Hz, f), 16.44 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.98 ppm; IR (neat) 2989 (aromatic C-H), 2904 (aliphatic C-H), 1601 (C=C), 1494 (aromatic C=C), 1453 (aromatic C=C), 1442 (aromatic C=C), 1391 (aromatic C=C), 1249 (P=O), 1048 (C-O), 1023 (C-O), 956 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{21}H_{27}O_3P$ = 358.1698, found 358.1685 *m/z*.

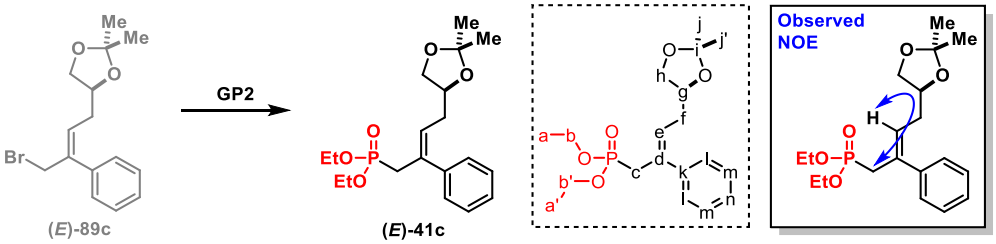


Synthesis of phosphonate functionalized alkene (*Z*)-41b: Following **GP2**, allyl bromide (*E*)-**89b** (317 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*Z*)-**41b** (326 mg, 87%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; $[\alpha]_D^{20}$ = +25.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, dd, *J* = 5.2, 1.2 Hz, n), 7.07 (1H, dd, *J* = 3.6, 0.8 Hz, l), 7.02 (1H, dd, *J* = 5.2, 3.6 Hz, m), 5.79 (1H, dd, *J* = 12.8, 7.0 Hz, e), 4.21-3.96 (6H, m, b+b'+g+h(1H)), 3.57 (1H, dd, *J* = 8.0, 7.0 Hz, h(1H)), 2.99 (2H, d, $^2J_{P\text{-}H}$ = 21.6 Hz, c), 2.64-2.58 (2H, m, f), 1.42 (3H, s, j or j'), 1.36 (3H, s, j or j'), 1.24 (3H, t, *J* = 7.0 Hz, a or a'), 1.23 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.46 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, d), 128.87 (d, $^3J_{C\text{-}P}$ = 11 Hz, e), 127.06 (l or m), 126.98 (l or m), 126.12 (d, $^3J_{C\text{-}P}$ = 11 Hz, k), 125.35 (n), 109.25 (i), 75.62 (d, $^5J_{C\text{-}P}$ = 3 Hz, g), 69.17 (h), 62.10 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b+b'), 37.15 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 34.02 (d, $^4J_{C\text{-}P}$ = 2.0 Hz, f), 27.05 (j or j'), 25.84 (j or j'), 16.53 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.20 ppm; Proof of stereochemistry: Strong NOE is observed between vinyl hydrogen (H_e) and the methylene hydrogens adjacent to phosphonate functionality (H_c). IR (neat) 2983 (aromatic C-H), 2905 (aliphatic C-H), 1368 (aromatic C=C), 1248 (P=O), 1022 (C-O), 958 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{27}O_5PS + Na^+$ = 397.1215, found 397.1218 *m/z*.



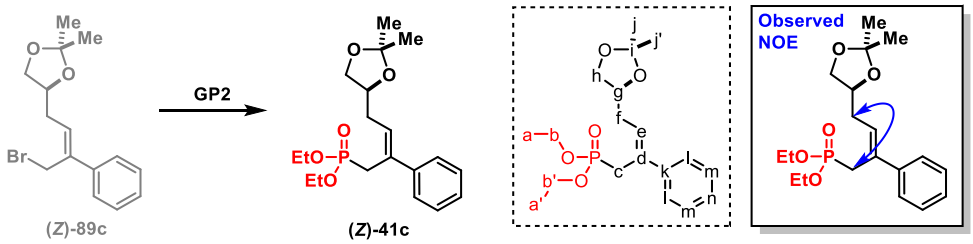
Synthesis of phosphonate functionalized alkene (*E*)-42b: Following **GP2**, allyl bromide (*Z*)-**89b** (158 mg, 0.50 mmol, 1.00 eq) yields the alkene substrate (*E*)-**42b** (150 mg, 80%)

as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; $[\alpha]_D^{20}$ = +7.0° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (1H, d, *J* = 5.0 Hz, n), 7.09 (1H, d, *J* = 3.5 Hz, l), 6.96 (1H, dd, *J* = 5.0, 3.5 Hz, m), 6.12 (1H, dd, *J* = 13.5, 7.0 Hz, e), 4.29-4.23 (1H, m, g), 4.10-3.95 (5H, m, b+b'+h(1H)), 3.65 (1H, dd, *J* = 8.0, 7.0 Hz, h(1H)), 3.08 (2H, d, $^2J_{P\text{-}H}$ = 22.0 Hz, c), 2.66-2.53 (2H, m, f), 1.45 (3H, s, j or j'), 1.37 (3H, s, j or j'), 1.22 (3H, t, *J* = 7.0 Hz, a or a'), 1.21 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.93 (d, $^3J_{C\text{-}P}$ = 3.0 Hz, d), 127.46 (m), 126.29 (d, $^3J_{C\text{-}P}$ = 11.0 Hz, e & k), 124.00 (l), 123.97 (n), 109.24 (i), 75.34 (d, $^5J_{C\text{-}P}$ = 3.0 Hz, g), 69.05 (h), 62.27 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 62.23 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 33.17 (d, $^4J_{C\text{-}P}$ = 3.0 Hz, f), 29.58 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 27.04 (j or j'), 25.80 (j or j'), 16.48 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.78 ppm; Proof of stereochemistry: Strong NOE is observed between methylene hydrogens H_f and the methylene hydrogens adjacent to phosphonate functionality H_c. IR (neat) 2985 (aromatic C-H), 2903 (aliphatic C-H), 1370 (aromatic C=C), 1248 (P=O), 1023 (C-O), 957 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{27}O_5PS+Na^+$ = 397.1215, found 397.1214 *m/z*.



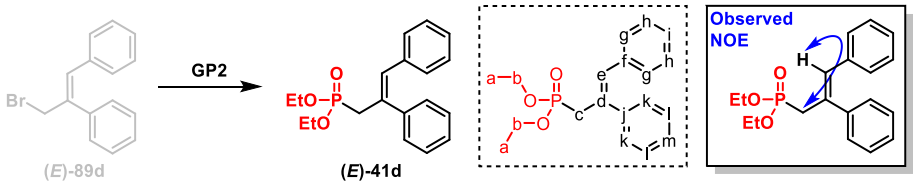
Synthesis of phosphonate functionalized alkene (*E*)-41c: Following **GP2**, allyl bromide (*E*)-**89c** (311 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*E*)-**41c** (313 mg, 85%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; $[\alpha]_D^{20}$ = +17.9° (*c* = 1.0, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 7.35-7.24 (5H, m, aryl), 5.75 (1H, dd, *J* = 13.3,

7 Hz, e), 4.12-4.09 (1H, m, g), 4.00-3.89 (5H, m, b+b'+h(1H)), 3.49 (1H, t, J = 7.7 Hz, h(1H)), 2.95 (2H, d, $^{2}J_{P\text{-}H}$ = 21.7 Hz, c), 2.20-2.46 (2H, m, f), 1.37 (3H, s, j or j'), 1.34 (3H, s, j or j'), 1.21-1.17 (6H, m, a+a') ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 140.05 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz, d), 133.65 (d, $^{3}J_{C\text{-}P}$ = 10.5 Hz, k), 128.77 (aryl), 128.34 (aryl), 127.28 (d, $^{3}J_{C\text{-}P}$ = 10.5 Hz, e), 109.11 (i), 75.67 (d, $^{5}J_{C\text{-}P}$ = 5.25 Hz, g), 69.15 (h), 61.89 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.85 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 36.51 (d, $^{1}J_{C\text{-}P}$ = 138.5 Hz, c), 33.60 (d, $^{4}J_{C\text{-}P}$ = 1.75 Hz, f), 26.99 (j or j'), 25.83 (j or j'), 16.47 (d, $^{3}J_{C\text{-}P}$ = 7 Hz, a or a'), 16.45 (d, $^{3}J_{C\text{-}P}$ = 7 Hz, a or a') ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 26.59 ppm; Proof of stereochemistry: Strong NOE is observed between vinyl hydrogen (H_e) and the methylene hydrogens adjacent to phosphonate functionality (H_c). IR (neat) 2982 (aromatic C-H), 2904 (aliphatic C-H), 1600 (C=C), 1442 (aromatic C=C), 1368 (aromatic C=C), 1249 (P=O), 1048 (C-O), 1023 (C-O), 957 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{19}H_{29}O_5P$ = 368.1753, found 368.1767 *m/z*.



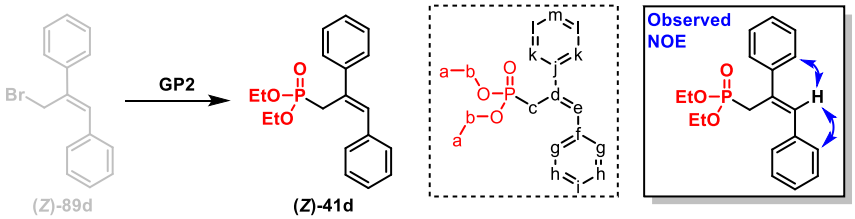
Synthesis of phosphonate functionalized alkene (*Z*)-41c: Following **GP2**, allyl bromide (*Z*)-**89c** (311 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*Z*)-**41c** (321 mg, 87%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; $[\alpha]_D^{20}$ = +7.3° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.44-7.25 (5H, m, aryl), 5.94 (1H, dd, J = 13.3, 6.3 Hz, e), 4.28 (1H, m, g), 4.30-4.09 (1H, m, h(1H)), 4.01-3.95 (2H, m, b or b'), 3.94-3.87 (2H, m, b or b'), 3.69-3.67 (1H, m, h(1H)), 3.13 (2H, d, $^{2}J_{P\text{-}H}$ = 22.4 Hz, c), 2.67-2.60 (2H,

m, f), 1.46 (3H, s, j or j'), 1.38 (3H, s, j or j'), 1.18-1.16 (6H, m, a+a') ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 142.47 (d, $^{2}J_{C\text{-}P}$ = 1.75 Hz, d), 132.74 (d, $^{3}J_{C\text{-}P}$ = 12.25 Hz, k), 128.45 (aryl), 127.84 (d, $^{3}J_{C\text{-}P}$ = 12.25 Hz, k), 127.42 (aryl), 126.80 (aryl), 109.23 (i), 75.57 (d, $^{5}J_{C\text{-}P}$ = 1.75 Hz, g), 69.16 (h), 62.06 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 62.02 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 33.52 (d, $^{4}J_{C\text{-}P}$ = 3.50 Hz, f), 29.28 (d, $^{1}J_{C\text{-}P}$ = 138.25 Hz, c), 27.13 (j or j'), 25.84 (j or j'), 16.44 (d, $^{3}J_{C\text{-}P}$ = 7 Hz, a+a') ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 26.42 ppm; Proof of stereochemistry: Strong NOE is observed between methylene hydrogens H_f and the methylene hydrogens adjacent to phosphonate functionality H_c. IR (neat) 2983 (aromatic C-H), 2903 (aliphatic C-H), 1599 (C=C), 1444 (aromatic C=C), 1368 (aromatic C=C), 1248 (P=O), 1052 (C-O), 1023 (C-O), 957 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{19}H_{29}O_5P+Na^+$ = 391.1650, found 391.1649 *m/z*.



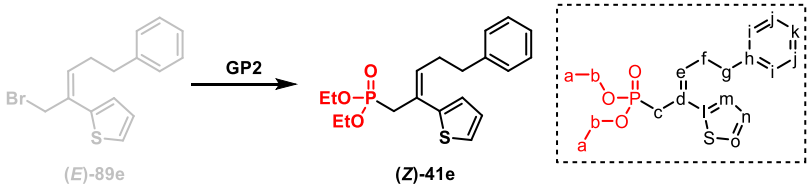
Synthesis of phosphonate functionalized alkene (*E*)-41d: Following **GP2**, allyl bromide (*E*)-**89d** (273 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*E*)-**41d** (281 mg, 85%) as a light buff oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (5H, m, aryl), 7.13-7.11 (3H, m, aryl), 6.99-6.97 (2H, m, aryl), 6.70 (2H, d, $^{4}J_{P\text{-}H}$ = 6.0 Hz, e), 4.10-3.94 (4H, m, b), 3.09 (2H, d, $^{2}J_{C\text{-}P}$ = 22 Hz, c), 1.23 (6H, t, *J* = 7.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.70 (d, $^{2}J_{C\text{-}P}$ = 4.0 Hz, d), 136.96 (d, $^{4}J_{C\text{-}P}$ = 4.0 Hz, f), 132.66 (d, $^{3}J_{C\text{-}P}$ = 12 Hz, j), 131.16 (d, $^{3}J_{C\text{-}P}$ = 12 Hz, e), 129.29 (aryl), 129.26 (aryl), 129.11 (aryl), 129.09 (aryl), 128.64 (aryl), 128.06 (aryl), 127.50 (aryl), 126.86 (aryl), 62.05 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b), 37.56 (d, $^{1}J_{C\text{-}P}$ = 137 Hz, c), 16.52 (d, $^{3}J_{C\text{-}P}$ = 6.5

Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.31 ppm; Proof of stereochemistry: Strong NOE is observed between vinyl hydrogen (H_e) and the methylene hydrogens adjacent to phosphonate functionality (H_c). IR (neat) 2979 (aromatic C-H), 2905 (aliphatic C-H), 1598 (C=C), 1493 (aromatic C=C), 1443 (aromatic C=C), 1390 (aromatic C=C), 1248 (P=O), 1055 (C-O), 1019 (C-O), 957 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{19}H_{23}O_3P$ = 330.1385, found 330.1384 *m/z*.

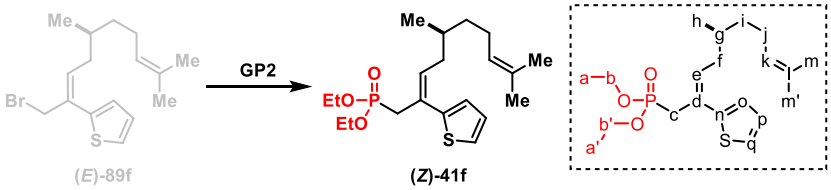


Synthesis of phosphonate functionalized alkene (*Z*)-41d: Following **GP2**, allyl bromide (*Z*)-**89d** (273 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*Z*)-**41d** (274 mg, 83%) as a light buff oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.0 Hz, g or k), 7.51 (2H, d, *J* = 8.0 Hz, g or k), 7.41-7.35 (4H, m, aryl), 7.32-7.26 (2H, m, aryl), 6.90 (1H, d, $^4J_{P\text{-}H}$ = 5.25 Hz, e), 3.97-3.75 (4H, m, b), 3.34 (2H, d, *J* = 22.4 Hz, c), 1.09 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.41 (d, $^4J_{C\text{-}P}$ = 2.0 Hz, f), 137.16 (d, $^2J_{C\text{-}P}$ = 3.5 Hz, d), 132.77 (d, $^3J_{C\text{-}P}$ = 11 Hz, j), 132.33 (d, $^3J_{C\text{-}P}$ = 13 Hz, e), 128.88 (aryl), 128.86 (aryl), 128.37 (aryl), 128.24 (aryl), 127.49 (aryl), 127.16 (aryl), 126.81 (aryl), 61.63 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b), 29.15 (d, $^1J_{C\text{-}P}$ = 140.11 Hz, c), 16.09 (d, $^3J_{C\text{-}P}$ = 6.4 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.33 ppm; Proof of stereochemistry: Strong NOE is observed between vinyl hydrogen (H_e) and the ortho hydrogens of the aromatic ring (H_g and H_k). IR (neat) 2979 (aromatic C-H), 2904 (aliphatic C-H), 1599 (C=C), 1494 (aromatic C=C), 1444 (aromatic C=C), 1391 (aromatic

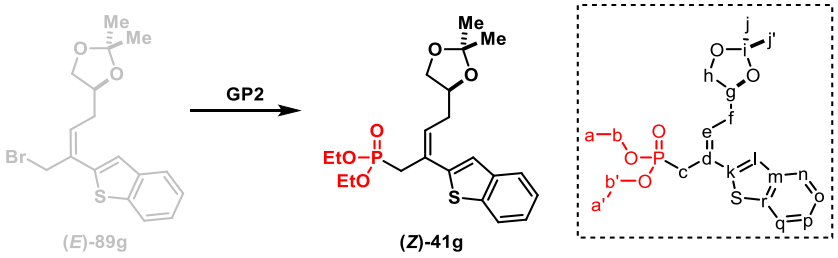
C=C), 1245 (P=O), 1053 (C-O), 1023 (C-O), 957 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{19}H_{23}O_3P+Na^+$ = 353.1283, found 353.1285 *m/z*.



Synthesis of phosphonate functionalized alkene (*Z*)-41e: Following **GP2**, allyl bromide (*E*)-**89e** (307 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*Z*)-**41e** (295 mg, 81%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (3H, m, aryl), 7.22-7.18 (3H, m, aryl), 7.02-7.00 (2H, m, m+n), 5.82 (1H, dd, *J* = 12.5, 7.0 Hz, e), 4.08-3.92 (4H, m, b), 2.98 (2H, d, $^2J_{P-H}$ = 21.5 Hz, c), 2.78 (2H, t, *J* = 7.5 Hz, g), 2.68-2.61 (2H, m, f), 1.23 (6H, t, *J* = 7.0 Hz, a) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.75 (d, $^2J_{C-P}$ = 4.0 Hz, d), 141.65 (h), 133.49 (d, $^3J_{C-P}$ = 11.0 Hz, e), 128.63 (aryl), 128.52 (aryl), 126.85 (aryl), 126.70 (aryl), 126.10 (aryl), 125.07 (aryl), 124.02 (d, $^3J_{C-P}$ = 11.0 Hz, l), 62.04 (d, $^2J_{C-P}$ = 7.0 Hz, b), 36.90 (d, $^1J_{C-P}$ = 139 Hz, c), 36.00 (d, $^5J_{C-P}$ = 3.5 Hz, g), 31.66 (d, $^4J_{C-P}$ = 3.0 Hz, f), 16.51 (d, $^3J_{C-P}$ = 6.5 Hz, a) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.55 ppm; IR (neat) 2983 (aromatic C-H), 2904 (aliphatic C-H), 1605 (C=C), 1494 (aromatic C=C), 1368 (aromatic C=C), 1249 (P=O), 1023 (C-O), 957 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{19}H_{25}O_3PS$ = 364.1262, found 364.1253 *m/z*.

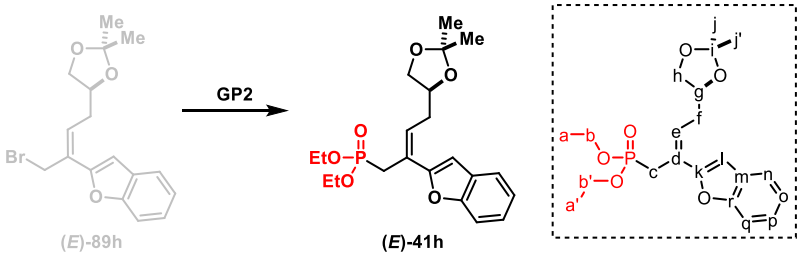


Synthesis of phosphonate functionalized alkene (*Z*)-41f: Following **GP2**, allyl bromide (*E*)-**89f** (327 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*Z*)-**41f** (308 mg, 80%) as a light buff oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +24.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (1H, m, q), 7.04-7.00 (2H, m, o+p), 5.78 (1H, dd, *J* = 13.0, 7.0 Hz, e), 5.09 (1H, t, *J* = 7.0 Hz, k), 4.08-3.93 (4H, m, b+b'), 2.98 (2H, d, $^2J_{P\text{-}H}$ = 21.2 Hz, c), 2.35-2.11 (2H, m, f), 2.05-1.89 (2H, m, j), 1.68 (3H, s, m or m'), 1.63-1.55 (1H, m, g), 1.60 (3H, s, m or m'), 1.42-1.32 (1H, m, i), 1.23 (6H, t, *J* = 7.0 Hz, a+a'), 1.26-1.13 (1H, m, i), 0.92 (3H, d, *J* = 7.0 Hz, h) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.12 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, d), 133.82 (d, $^3J_{C\text{-}P}$ = 11.0 Hz, e), 131.35 (l), 126.75 (*o* or p), 126.64 (*o* or p), 124.91 (k), 126.64 (d, $^4J_{C\text{-}P}$ = 1.0 Hz, o), 123.74 (d, $^3J_{C\text{-}P}$ = 11.0 Hz, n), 61.98 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b+b'), 36.98 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 36.99 (d, $^4J_{C\text{-}P}$ = 3.0 Hz, f), 36.97 (i), 33.49 (d, $^5J_{C\text{-}P}$ = 3.0 Hz, g), 25.89 (m or m'), 25.74 (j), 19.74 (h), 17.81 (m or m'), 16.51 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, d) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.77 ppm; IR (neat) 2963 (aromatic C-H), 2907 (aliphatic C-H), 1440 (aromatic C=C), 1377 (aromatic C=C), 1252 (P=O), 1051 (C-O), 1025 (C-O), 957 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{20}H_{33}O_3PS$ = 384.1888, found 384.1897 *m/z*.



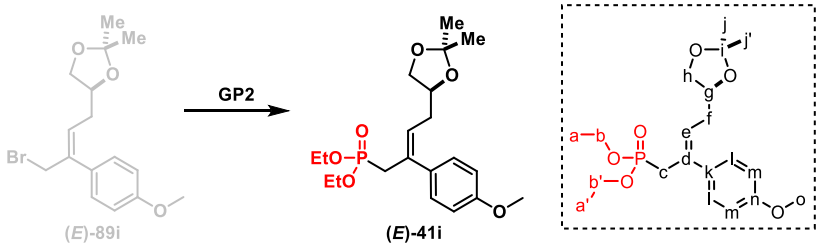
Synthesis of phosphonate functionalized alkene (*Z*)-41g: Following **GP2**, allyl bromide (*E*)-**89g** (367 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*Z*)-**41g** (378 mg, 89%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +13.8° (*c* = 1.0, $CHCl_3$);

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* =8.8 Hz, q), 7.76 (1H, d, *J* = 7.7 Hz, l), 7.37-7.29 (3H, m, n+o+p), 5.93 (1H, dd, *J* = 12.6, 7.0 Hz, e), 7.23-7.20 (1H, m, g), 4.08-4.00 (5H, m, b+b'+h(1H)), 3.59 (1H, dd, *J* = 7.7, 7.0 Hz, h(1H)), 3.05 (2H, d, $^{2}J_{P\text{-}H}$ = 21 Hz, c), 2.71-2.61 (2H, m, f), 1.43 (3H, s, j or j'), 1.37 (3H, s, j or j'), 1.24-1.21 (6H, m, a+a') ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 141.67 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz, d), 139.90 (m or *r*), 139.70 (m or *r*), 130.70 (d, $^{3}J_{C\text{-}P}$ = 10.5 Hz, e), 126.51 (d, $^{3}J_{C\text{-}P}$ = 10.5 Hz, k), 124.58 (aryl), 123.83 (aryl), 123.79 (aryl), 122.20 (q), 109.32 (i), 75.55 (d, $^{5}J_{C\text{-}P}$ = 1.72 Hz, g), 69.18 (h), 62.21 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 62.19 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 36.78 (d, $^{1}J_{C\text{-}P}$ = 136.5 Hz, c), 34.06 (d, $^{4}J_{C\text{-}P}$ = 1.75 Hz, f), 27.06 (j or j'), 25.84 (j or j'), 16.55 (d, $^{3}J_{C\text{-}P}$ = 7.0 Hz, a or a'), 16.53 (d, $^{3}J_{C\text{-}P}$ = 7.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.96 ppm; IR (neat) 2982 (aromatic C-H), 2904 (aliphatic C-H), 1661 (C=C), 1456 (aromatic C=C), 1437 (aromatic C=C), 1248 (P=O), 1052 (C-O), 1022 (C-O), 958 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{21}H_{29}O_5PS$ = 424.1473, found 424.1453 *m/z*.



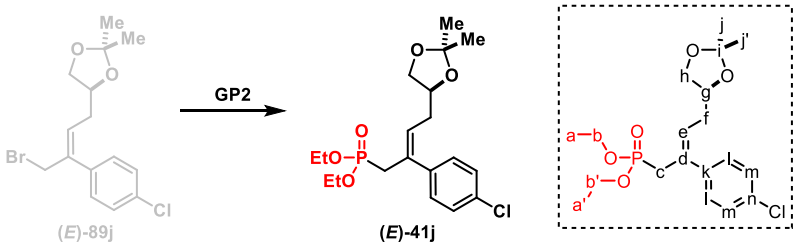
Synthesis of phosphonate functionalized alkene (*E*)-41h: Following **GP2**, allyl bromide (*E*)-**89h** (351 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*E*)-**41h** (319 mg, 78%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.6; $[\alpha]_D^{20}$ = +5.45° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.57 (1H, d, *J* = 7.7 Hz, n), 7.46 (1H, d, *J* = 8.4 Hz, q), 7.31-7.28 (1H, m, *o* or q), 7.24 (1H, dd, *J* = 7.7, 7.0 Hz, *o* or q), 6.82 (1H, s, l), 5.90 (1H, dd, *J* = 12.6, 7.0 Hz, e), 4.32-4.28 (1H, m, g), 4.11 (1H, dd, *J* = 7.7, 6.3 Hz, h(1H)), 4.09-4.00

(4H, m, b+b'), 3.67 (1H, t, J = 7.7 Hz, h(1H)), 3.08 (2H, d, $^{2}J_{P\text{-}H}$ = 21.7 Hz, c), 2.94-2.87 (2H, m, f), 1.46 (3H, s, j or j'), 1.39 (3H, s, j or j'), 1.23-1.20 (6H, m, a+a') ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.63 (d, $^{2}J_{C\text{-}P}$ = 4.50 Hz, d), 154.45 (r), 130.90 (d, $^{3}J_{C\text{-}P}$ = 11.0 Hz, e), 128.56 (m), 124.79 (*o* or p), 123.11 (*o* or p), 122.27 (d, $^{3}J_{C\text{-}P}$ = 10.5 Hz, k), 121.28 (n), 111.22 (q), 109.34 (i), 106.50 (l), 75.65 (d, $^{5}J_{C\text{-}P}$ = 3.5 Hz, g), 69.23 (h), 62.22 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b+b'), 34.11 (d, $^{4}J_{C\text{-}P}$ = 1.75 Hz, f), 33.24 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 27.11 (j or j'), 25.89 (j or j'), 16.54 (d, $^{3}J_{C\text{-}P}$ = 6.50 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.35 ppm; IR (neat) 2981 (aromatic C-H), 2904 (aliphatic C-H), 1474 (aromatic C=C), 1369 (aromatic C=C), 1252 (P=O), 1048 (C-O), 1022 (C-O), 960 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{21}H_{29}O_6P$ = 408.1702, found 408.1710 *m/z*.



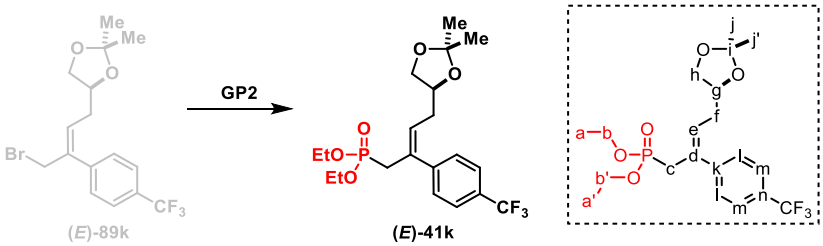
Synthesis of phosphonate functionalized alkene (*E*)-41i: Following **GP2**, allyl bromide (*E*)-**89i** (341 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*E*)-**41i** (311 mg, 78%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +13.8° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.18 (2H, d, J = 8.4 Hz, l), 6.88 (2H, d, J = 8.4 Hz, m), 5.71 (1H, dd, J = 13.3, 7.0 Hz, e), 4.12-4.09 (1H, m, g), 4.03-3.91 (5H, m, b+b'+h(1H)), 3.83 (3H, s, o), 3.49 (1H, dd, J = 7.7, 7.0 Hz, h(1H)), 2.97-2.89 (2H, m, c), 2.43-2.27 (2H, m, f), 1.38 (3H, s, j or j'), 1.35 (3H, s, j or j'), 1.22 (3H, t, J = 7.0 Hz, a or a'), 1.21 (3H, t, J = 7.0 Hz, a or a') ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.82 (n), 133.16 (d, $^{3}J_{C\text{-}P}$ = 10.5 Hz, k), 132.36 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz, d), 129.93 (l), 126.90 (d, $^{3}J_{C\text{-}P}$ = 12.25 Hz, e), 113.73 (m),

109.11 (i), 75.74 (d, $^{3}J_{C\text{-}P}$ = 3.5 Hz, g), 69.18 (h), 61.90 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 61.87 (d, $^{2}J_{C\text{-}P}$ = 5.25 Hz, b or b'), 55.45 (o), 36.61 (d, $^{1}J_{C\text{-}P}$ = 137 Hz, c), 33.66 (d, $^{4}J_{C\text{-}P}$ = 3.50 Hz, f), 27.02 (j or j'), 25.85 (j or j'), 16.53 (d, $^{3}J_{C\text{-}P}$ = 7.0 Hz, a or a'), 16.52 (d, $^{3}J_{C\text{-}P}$ = 5.25 Hz, a or a') ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 26.82 ppm; IR (neat) 2983 (aromatic C-H), 2905 (aliphatic C-H), 1608 (C=C), 1512, 1456 (aromatic C=C), 1368 (aromatic C=C), 1244 (P=O), 1024 (C-O), 958 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{20}H_{31}O_6P$ = 398.1858, found 398.1874 *m/z*.



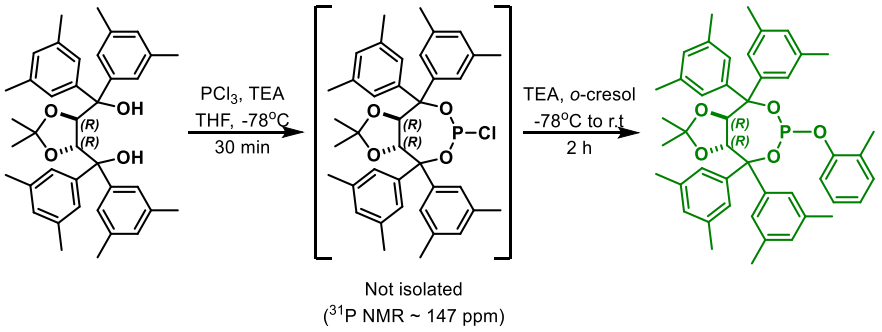
Synthesis of phosphonate functionalized alkene (*E*)-41j: Following **GP2**, allyl bromide (*E*)-**89j** (346 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*E*)-**41j** (326 mg, 81%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +21.9° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.4 Hz, m), 7.20 (2H, d, *J* = 8.4 Hz, l), 5.76 (1H, dd, *J* = 13.0, 7.0 Hz, e), 4.11-3.92 (6H, m, b+b'+g+h(1H)), 3.49-3.45 (1H, m, h(1H)), 2.90 (2H, d, $^{2}J_{P\text{-}H}$ = 21.6 Hz, c), 2.34-2.23 (2H, m, f), 1.37 (3H, s, j or j'), 1.33 (3H, s, j or j'), 1.23-1.19 (6H, m, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.49 (d, $^{2}J_{C\text{-}P}$ = 4.0 Hz, d), 133.20 (n), 132.61 (d, $^{3}J_{C\text{-}P}$ = 11 Hz, k), 130.22 (d, $^{4}J_{C\text{-}P}$ = 1.75 Hz, l), 128.54 (m), 128.08 (d, $^{3}J_{C\text{-}P}$ = 12 Hz, e), 109.19 (i), 75.51 (d, $^{5}J_{C\text{-}P}$ = 3.0 Hz, g), 69.10 (h), 61.97 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 61.94 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 36.44 (d, $^{1}J_{C\text{-}P}$ = 137 Hz, c), 33.65 (d, $^{4}J_{C\text{-}P}$ = 4.0 Hz, f), 26.99 (j or j'), 25.79 (j or j'), 16.49 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.23 ppm; IR (neat) 2983 (aromatic C-H), 2904 (aliphatic C-

H), 1595 (C=C), 1491 (aromatic C=C), 1369 (aromatic C=C), 1248 (P=O), 1024 (C-O), 958 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{19}H_{28}ClO_5P$ = 402.1363, found 402.1349 *m/z*.



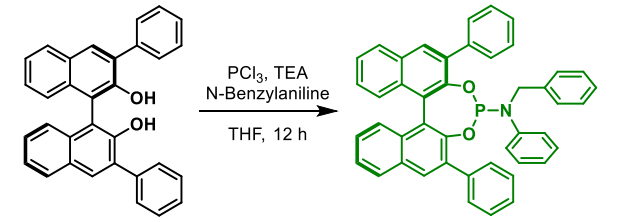
Synthesis of phosphonate functionalized alkene (*E*)-41k: Following **GP2**, allyl bromide (*E*)-**89k** (379 mg, 1.00 mmol, 1.00 eq) yields the alkene substrate (*E*)-**41k** (319 mg, 73%) as a light buff colored oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; $[\alpha]_D^{20}$ = +19° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.0 Hz, m), 7.39 (2H, d, *J* = 8.0 Hz, m), 5.82 (1H, dd, *J* = 13.0, 7.0 Hz, e), 4.16-3.90 (6H, m, b+b'+g+h(1H)), 3.49 (1H, dd, *J* = 7.6, 7.2 Hz, h(1H)), 2.93 (2H, d, $^2J_{P\text{-}H}$ = 21.6 Hz, c), 2.27-2.20 (2H, m, f), 1.37 (3H, s, j or j'), 1.34 (3H, s, j or j'), 1.22-1.17 (6H, m, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.86 (d), 132.62 (d, $^3J_{C\text{-}P}$ = 11 Hz, k), 129.53 (q, $^2J_{C\text{-}F}$ = 32 Hz, n), 129.26 (d, $^4J_{C\text{-}P}$ = 2.0 Hz, l), 128.73 (d, $^3J_{C\text{-}P}$ = 12 Hz, e), 125.34 (q, $^3J_{C\text{-}F}$ = 4 Hz, m), 124.32 (q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 109.26 (i), 75.43 (d, $^5J_{C\text{-}P}$ = 4.0 Hz, g), 69.08 (h), 62.01 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.98 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 36.39 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 33.68 (d, $^4J_{C\text{-}P}$ = 3.0 Hz, f), 26.98 (j or j'), 25.77 (j or j'), 16.46 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.44 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.93 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.59 ppm; IR (neat) 2984 (aromatic C-H), 2905 (aliphatic C-H), 1616 (C=C), 1369 (aromatic C=C), 1323 (C-F), 1249 (P=O), 1024 (C-O), 959 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{20}H_{28}F_3O_5P$ = 436.1626, found 436.1636 *m/z*.

5.3. Ligand synthesis



Procedure for preparation of TADDOL-derived phosphite L2: *xylyl*-TADDOL was prepared as previously reported by Seebach.[8] The preparation of the chiral phosphite is done according to previously reported procedure[9] with the following modifications: A solution of *xylyl*-TADDOL (500 mg, 0.864 mmol, 1.00 eq) and triethylamine (TEA; 0.48 mL, 3.4 mmol, 4.0 eq) in dry THF (35 mL) was cooled to –78° C using a dry-ice acetone bath and to the resulting mixture was added PCl_3 (70 µL, 0.86 mmol, 1.0 eq) rapidly in one portion. The resultant mixture was stirred for 30 minutes at –78°C. At this point, the crude ^{31}P NMR spectrum showed the disappearance of the PCl_3 peak at ~220 ppm and the appearance of a new peak at ~147 ppm which indicates the presence of the intermediate $(RO)_2P–Cl$ in solution. To the resultant reaction mixture at –78°C, triethylamine (0.48 mL, 3.4 mmol, 4.0 eq) and neat *o*-cresol (90 µL, 0.86 mmol, 1.0 eq) were sequentially added in single portions. The mixture was allowed to warm up to room temperature and stirred for a total of *ca.* 2 hours. The completion of reaction is indicated by the disappearance of the peak at ~147 ppm and appearance of a new peak at ~131 ppm in the crude ^{31}P NMR spectrum of the final reaction mixture. Afterwards the mixture was filtered over Celite and the volatiles were removed under reduced pressure. Flash chromatography on silica gel (ethyl-acetate/hexanes 95:5) afforded *(R,R)*-**T2** as a foamy white solid (464 mg, 75%):

Melting point = 88-92ºC; TLC analysis (ethyl-acetate/hexanes 95:5) R_f = 0.5; $[\alpha]_D^{20}$ = –90.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.35-6.88 (16H, m, aryl), 5.17 (1H, d, *J* = 8.4 Hz), 5.09 (1H, d, *J* = 8.4 Hz), 2.35 (12H, s), 2.29 (6H, s), 2.26 (6H, s), 2.10 (3H, s), 1.13 (3H, s), 0.62 (3H, s) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) δ 150.79, 146.39 (d, J_{C-P} = 2 Hz), 141.25 (d, J_{C-P} = 2 Hz), 140.86, 137.70, 137.22, 136.98, 136.66, 130.97, 130.05 (d, J_{C-P} = 3 Hz), 129.37, 129.16, 129.02, 128.84, 126.71, 126.66, 126.37, 125.04, 124.93, 123.72, 120.69, 120.57, 112.65, 84.77 (d, J_{C-P} = 6 Hz), 83.79, 82.83 (d, J_{C-P} = 16 Hz), 82.09 (d, J_{C-P} = 4 Hz), 26.97, 25.97, 21.37, 21.31, 21.22, 16.46 ppm; ^{31}P NMR (162 MHz, CD_2Cl_2) δ 133.40 ppm; IR (neat) 2915 (aromatic C-H), 2864.04 (aliphatic C-H), 1601, 1489, 1455, 1371, 1216 (C-O-C), 1159, 1035, 939 cm^{-1}; HRMS (ESI) calculated for $C_{46}H_{51}O_5P+Na^+$ 737.3372, found 737.3378 *m/z*.



Procedure for preparation of BINOL-derived phosphoramidite B2: (*R*)-(3,3'-bis(Ph))-BINOL is prepared as previously reported.[10] The chiral cyclic phosphoramidite (*R*)-(3,3'-bis(Ph))-BINOL-PN(Bn)Ph (**B2**) is prepared according to previously reported procedure[11] from our lab as follows: PCl_3 (0.26 mL, 1.1 equiv, 3.00 mmol) is added dropwise to a solution of N-Benzylaniline (549 mg, 1.10 equiv, 3.00 mmol) and triethylamine (TEA; 0.70 mL, 1.85 equiv, 5.00 mmol) in dry THF (20 mL) under nitrogen at room temperature. The resultant mixture is refluxed for 6 hours, then cooled down to room temperature and eventually to -78ºC using a dry ice-acetone bath. A solution of (*R*)-(3,3'-bis(Ph))-BINOL

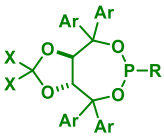
(1.20 mg, 2.73 mmol, 1.00 equiv) and TEA (1.36 mL, 9.80 mmol, 3.60 equiv) in THF (20 mL) is then added drop-wise to the reaction mixture. The resultant mixture is allowed to slowly warm up to room temperature and stir for a total of *ca.* 12 hours. Afterwards, the mixture is filtered over a bed of celite, celite bed washed with THF and the combined filtrates were concentrated in vacuum. Flash chromatography over silica gel (dichloromethane/hexanes 20:80) affords the title compound (1.24 g, 70%) as a foamy white solid: Melting point = 145-150 ºC; TLC analysis (dichloromethane/hexanes 20:80) R_f = 0.5; $[\alpha]_D^{20}$ = -210º (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, d, *J* = 12.5 Hz), 8.01 (2H, d, *J* = 8 Hz), 7.84-7.82 (2H, m), 7.73-7.72 (2H, m), 7.55-7.30 (12H, m), 7.13-7.06 (3H, m), 6.92-6.86 (5H, m), 6.18-6.15 (2H, m), 4.41 (1H, d, *J* = 15.5 Hz), 3.66 (1H, d, *J* = 15.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.22, 147.18, 146.98, 143.46, 143.20, 138.73, 138.31, 137.95, 135.34, 135.33, 134.68, 132.72, 132.51, 131.55, 131.11, 138.31, 137.95, 135.35, 135.33, 134.68, 132.72, 132.51, 131.55, 131.11, 130.66, 130.63, 130.49, 130.47, 130.33, 128.66, 128.61, 128.22, 128.07, 127.82, 127.79, 127.63, 127.23, 127.18, 126.70, 126.38, 125.57, 125.53, 125.47, 125.32, 124.78, 124.66, 124.19, 50.72, 50.67 ppm (**Note:** *Peak splitting in the ^{13}C NMR due to J_{C-P} was not feasible to resolve in this case because of the severity of peak overlap*.); ^{31}P NMR (162 MHz, $CDCl_3$) δ 135.99 ppm; HRMS (ESI) calculated for $C_{45}H_{32}NO_2P+Na^+$ = 672.2068, found 672.2082 *m/z*.

5.4. Ligand Screening Data

The data presented here is for the series of ligands that were tested on methylidene phosphonate substrate **5a**. Borane screening demonstrated pinacolborane is optimal for this

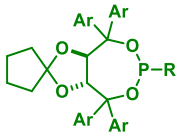
reaction as it yielded significant amounts of hydroboration products. Usage of tmdBH resulted in very high (*ca.* 40-50%) amounts of reduction side products and usage of catecholborane (catBH) resulted in uncatalyzed background reactions. The yields for ligand screenings were determined post CAHB via crude ^{31}P NMR analysis. The enantiomer ratios were determined after oxidation to the corresponding alcohols via chiral HPLC analysis. The ligand **T2** was chosen empirically from the screening data as the ligand of choice for subsequent development of the chemistry because of its superior performance as compared to the others tested.

Ligands screened:

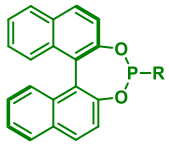


T1: X = Me; Ar = 3,5-Me_2-C_6H_3; R = OPh
T2: X = Me; Ar = 3,5-Me_2-C_6H_3; R = O(2-Me-C_6H_4)
T3: X = Me; Ar = 3,5-Me_2-C_6H_3; R = O(C_6F_5)
T4: X = Me; Ar = 3,5-Me_2-C_6H_3; R = O(1-naphthyl)
T5: X = Me; Ar = 3,5-Me_2-C_6H_3; R = O(2-naphthyl)
T6: X = Me; Ar = 3,5-Me_2-C_6H_3; R = O(3,4,5-$(OMe)_3$-C_6H_2)
T7: X = Me; Ar = Ph; R = OPh
T8: X = Me; Ar = 4-Me-C_6H_4; R = OPh
T9: X = Me; Ar = 4-*t*Bu-C_6H_4; R = OPh
T10: X = Me; Ar = 3,5-*i*Pr_2-C_6H_3; R = OPh
T11: X = Ph; Ar = 3,5-Me_2-C_6H_3; R = OPh

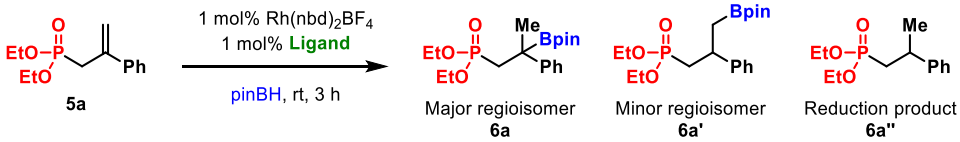
T12: X = Me; Ar = Ph; R = N(Me)Ph
T13: X = Me; Ar = 3,5-Me_2-C_6H_3; R = N(Me)Ph
T14: X = Me; Ar = 4-Me-C_6H_4; R = N(Bn)Ph
T15: X = Me; Ar = 4-*t*Bu-C_6H_4; R = N(Bn)Ph
T16: X = Ph; Ar = 3,5-Me_2-C_6H_3; R = N(Me)Ph



T17: Ar = Ph; R = OPh
T18: Ar = Ph; R = N(Me)Ph



B3: R = OPh
B4: R = N(Me)Ph



Summary of the screening results (Yields determined via crude ^{31}P NMR analysis):

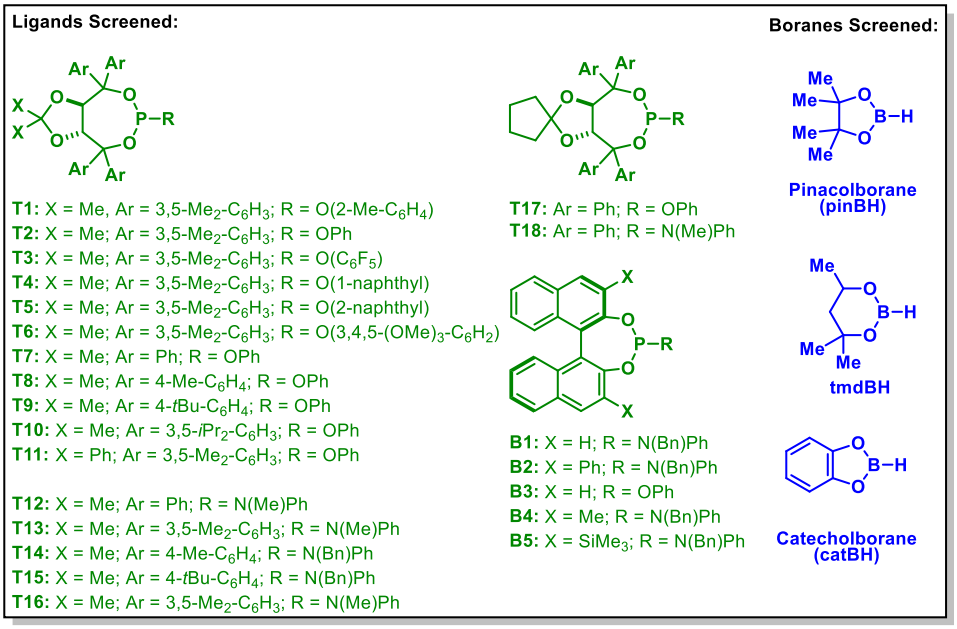
Entry	Ligand used	**5a** unreacted (%)	**6a** yield (%)	**6a** er	**6a'** yield (%)	**6a'** er	**6a:6a'** ratio	**6a''** yield (%)

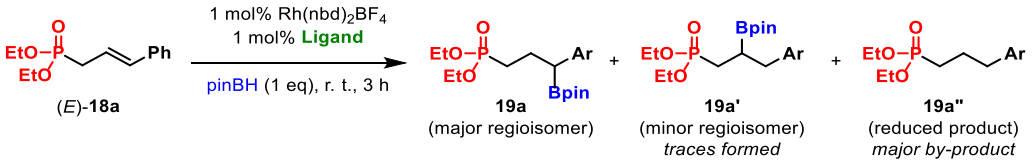
1	**T1**	0	81	95:5	13	92:8	6.2:1	5
2	**T2**	0	84	97:3	11	88:12	7.6:1	3
3	**T3**	0	48	63:37	49	82:18	1:1	3
4	**T4**	0	75	96:4	12	92:8	6.2:1	13
5	**T5**	0	65	68:32	25	88:12	2.5:1	9
6	**T6**	0	9	51:49	50	59:41	1:5.5	40
7	**T7**	0	75	92:8	13	64:36	5.6:1	12
8	**T8**	0	77	91:9	10	70:30	7.7:1	13
9	**T9**	0	69	94:6	12	63:37	5.3:1	19
10	**T10**	0	70	91:9	20	89:11	3.5:1	10
11	**T11**	0	75	92:8	11	88:12	6.8:1	12
12	**T12**	0	3	70:30	36	62:38	1:12	27
13	**T13**	0	4	56:44	32	76:24	1:8	18
14	**T14**	0	3	66:34	41	57:43	1:14	27
15	**T15**	0	14	52:48	45	53:47	1:3.1	28
16	**T16**	49	0	--	12	66:34	--	35
17	**T17**	0	73	90:10	14	65:35	5.3:1	13
18	**T18**	0	4	65:35	35	63:37	1:8.8	36
19	**B3**	10	0	--	45	48:52	--	42
20	**B4**	39	17	68:32	25	56:44	--	19
21	**BINAP**	100	--	--	--	--	--	--

As evident from Scheme 2.1, the TADDOL-derived chiral cyclic phosphites (with few exceptions) generally afford efficient enantioinduction for product **6a** from methylidene vinyl arene substrate **5a**. On the other hand, TADDOL-derived chiral cyclic phosphoramidites, BINOL-derived chiral cyclic phosphites and phosphoramidites generally afford poor levels of enantioinduction. The success of a specific ligand type in the directed-CAHB hinges significantly on the alkene's substitution pattern. While the

TADDOL-derived phosphites are remarkable for efficient enantioinduction for CAHB of methylidene vinyl arenes, the BINOL-derived phosphoramidites show superior selectivity for the isomeric 1,2-disubstituted vinyl arene substrates (Chapter 3).

The data presented below is a series of ligands that were screened on the substrate (*E*)-**18a** as part of the initial optimizations. Preliminary screening of boranes demonstrated the superior performance of pinacolborane (pinBH) over tmdBH in forming significant amounts of hydroboration products. With catecholborane (catBH), uncatalyzed background reactions were observed. The yields for the screening data are estimated from the ^{31}P NMR analysis of the crude CAHB mixtures. The enantiomer ratios are obtained after oxidation to the corresponding alcohols via chiral HPLC analysis. BINOL-derived phosphoramidite (*R*)-**B2** was empirically chosen as the ligand of choice for the subsequent development of chemistry because it gave the highest possible enantioinduction for product **19a** as compared to others tested. The major side product in the CAHB of (*E*)-**18a** is the alkene reduction product **19a"**. The minor regioisomer **19a'** is formed in trace quantities.





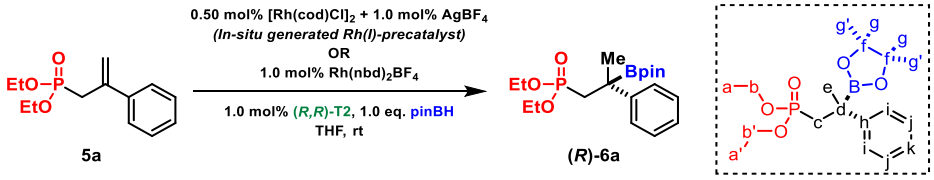
Summary of the small-scale (50 μmol substrate) screening results. (**Note:** Yields are estimated by ^{31}P NMR analysis of the crude reaction mixtures.)

Entry	Ligand Used	Unreacted (*E*)-**18a** (%)	Yield of **19a** (%)	Enantiomer Ratio of **19a**	Yield of **19a"** (%)	Ratio of **19a:19a"**	Total mass balance
1	**T1**	0	81	64:36	14	6:1	95
2	**T2**	0	82	48:52	9	9:1	91
3	**T3**	27	66	43:57	4	19:1	97
4	**T5**	3	77	34:66	17	5:1	97
5	**T6**	0	84	29:71	7	12:1	91
6	**T4**	0	68	40:60	17	4:1	85
7	**T11**	0	86	82:18	7	12:1	93
8	**T7**	7	82	79:21	11	7:1	100

9	**T8**	0	91	80:20	6	15:1	97
10	**T10**	0	82	29:71	13	6:1	95
11	**T9**	0	81	55:45	12	7:1	93
12	**T12**	0	87	58:42	5	17:1	92
13	**T13**	0	90	60:40	7	13:1	97
14	**T14**	0	86	61:39	8	11:1	94
15	**T15**	0	85	36:64	8	11:1	93
16	**T16**	0	89	59:41	9	10:1	98
17	**T17**	0	89	76:24	8	11:1	97
18	**T18**	0	91	59:41	6	15:1	97
19	**B1**	6	86	90:10	4	22:1	96
20	**B2**	0	87	97:3	10	9:1	97
21	**B3**	82	9	*Not determined*	9	1:1	100
22	**B4**	0	83	94:6	15	6:1	98
23	**B5**	0	80	95:5	17	5:1	97
24	**(*R*)-BINAP**	95	0	--	0	--	95
25	No catalyst	100	0	--	0	--	100

Note: Entry 25 is carried out to look for any background reaction of the substrate with pinacolborane in the absence of chiral rhodium catalyst under standard conditions.

5.5. General Procedure for Catalytic Asymmetric HydroBoration (CAHB) & Synthesis of Phosphonate-Functionalized Chiral Boronic Esters

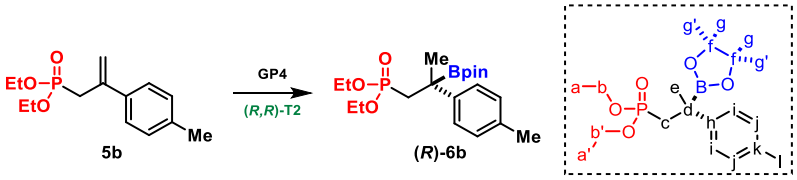


Representative procedure for Catalytic Asymmetric HydroBoration (CAHB) of conjugated methylidenes and trisubstituted alkenes (GP4): *Catalyst Preparation:* The active hydroboration catalyst is prepared in the dry nitrogen glovebox as follows: $[Rh(cod)Cl]_2$ (2.5 mg, 5.1 μmol) is dissolved in dry dichloromethane (0.5 mL) in an 8 mL glass vial equipped with a small teflon stirbar. To the resultant yellow/orange solution, a 0.05 *M* solution of $AgBF_4$ in THF (0.21 mL, 10.5 μmol) is added and the mixture is allowed to stir vigorously for 10 minutes at room temperature. The formed AgCl precipitate is filtered through a Pasteur pipette packed with cotton into a dry 8 mL vial and the cotton pack was further washed with additional 0.5 mL THF. The combined washings were dried in the vacuum chamber over 30 minutes. Following this, 1.02 mL of a stock solution of the ligand (*R*,*R*)-**T2** (Prepared by dissolving 8.65 mg of the ligand in 1.21 mL THF) is added to the dry Rh(I)-precursor and the resultant mixture is stirred vigorously for 15 minutes at room temperature to afford the active hydroboration catalyst. *Alternative Catalyst Preparation:* Alternatively, the catalyst can be prepared from $Rh(nbd)_2BF_4$ as follows: $Rh(nbd)_2BF_4$ (3.8 mg, 10 μmol) is weighed out in a dry 8 mL glass vial equipped with a small teflon stirbar and to the weighed crystals is added a 1.02 mL of a stock solution of the ligand (*R*,*R*)-**T2** (Prepared by dissolving 8.65 mg of the ligand in 1.21 mL THF). The resultant mixture is stirred vigorously for 1 hour to afford the active hydroboration catalyst. *Note:* In both the procedures above, the total volume of the active hydroboration catalyst is 1.02 mL which is about 1 mol% catalyst load for five 0.2 mmol CAHB reactions.

Catalysts prepared using either methods described above are comparable in their efficiencies for CAHB reactions.

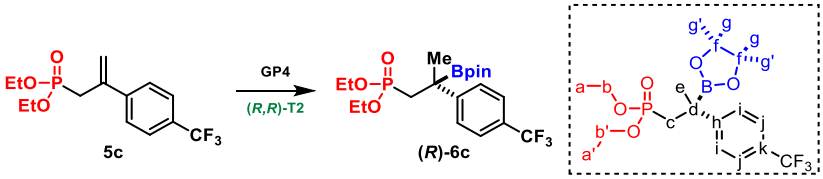
CAHB procedure: Substrate **5a** (51 mg, 0.2 mmol) is weighed out in a dry 8 mL vial charged with a small teflon stirbar. Dry THF (0.2 mL) is added, followed by neat pinacolborane (29 μL, 0.2 mmol, 1.0 eq) and the resultant mixture is stirred for 10 minutes. Afterwards, 0.2 mL of the chiral rhodium catalyst is added drop wise (over 10 minutes) and the reaction mixture is capped, taken outside of the glovebox and is stirred at room temperature (18 ^{o}C) for *ca.* 3 hours. The completion of the reaction is indicated by the disappearance of the starting material peak (~26 ppm) and the appearance of the product peak (~30 ppm) in the crude ^{31}P NMR spectrum of the reaction mixture. Afterwards, the reaction mixture is concentrated under reduced pressure and the crude mixture is purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:1) to afford the chiral tertiary benzylic boronic ester (*R*)-**6a** as a colorless oil (62 mg, 81%). [*Note:* Typical CAHB reactions were carried out with an overall substrate concentration of 0.5 M in THF and the typical reaction times were 3 hours at r.t. Gram scale reactions, however, were carried out with an overall substrate concentration of 1.0M in THF and with a reduced catalyst loading (0.5 mol%) and the reactions were run for 12 hours at r.t. Absolute configuration assignment: See section **9**. (*R*,*R*)-**T2** affords (*R*)-**6a**.] Characterization data for (*R*)-**6a**: TLC analysis (ethyl acetate/hexanes 2:3) R_f = 0.5; $[\alpha]_D^{20}$ = -3.9^{o} (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 7.5 Hz, i), 7.28 (2H, dd, *J* = 7.5, 7.0 Hz, j), 7.15 (1H, d, *J* = 7.0 Hz, k), 4.06-3.91 (4H, m, b+b'), 2.51-2.12 (2H, m, c), 1.58 (3H, s, e), 1.28-1.20 (18H, a+a'+g) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.28 (d, $^{3}J_{C\text{-}P}$ = 16.0 Hz, h), 128.30 (j), 126.67 (i), 125.68 (k), 83.93 (f), 61.32 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'),

60.95 (d, $^{2}J_{C\text{-}P}$ = 6 Hz, b or b'), 35.49 (d, $^{1}J_{C\text{-}P}$ = 138 Hz, c), 24.85 (g or g'), 24.71 (g or g'), 22.27 (d, $^{3}J_{C\text{-}P}$ = 4.0 Hz, e), 16.58 (d, $^{3}J_{C\text{-}P}$ = 5.0 Hz, a or a'), 16.53 (d, $^{3}J_{C\text{-}P}$ = 5.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.0 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.58 ppm; IR (neat) 2977 (aromatic C-H), 2931 (aliphatic C-H), 1495 (aromatic C=C), 1469 (aromatic C=C), 1444 (aromatic C=C), 1240 (P=O), 1053 (C-O), 1023 (C-O), 953 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{19}H_{32}BO_5P$ = 382.2080, found 382.2087 *m/z*. The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18a**.

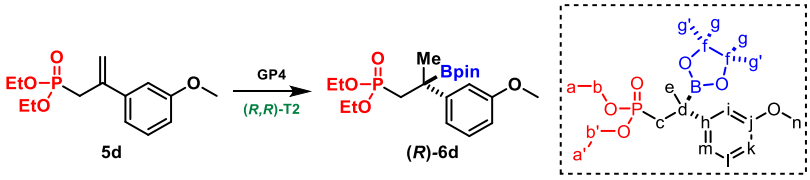


Synthesis of chiral tertiary benzylic boronic ester (*R*)-6b: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) using (*R*,*R*)-**T2**, the substrate **5b** (54 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6b** (64 mg, 81%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = -3.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.0 Hz, i), 7.09 (2H, d, *J* = 8.0 Hz, j), 4.09-3.90 (4H, m, b+b'), 2.46 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.30 (3H, s, l), 2.12 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.56 (3H, s, e), 1.28 (3H, t, *J* = 7.0 Hz, a or a'), 1.24 (3H, t, *J* = 3.0 Hz, a or a'), 1.20 (12H, s, g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.22 (d, $^{3}J_{C\text{-}P}$ = 16.0 Hz, h), 135.01 (k), 128.99 (j), 126.45 (i), 83.86 (f), 61.32 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 60.96 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 35.50 (d, $^{1}J_{C\text{-}P}$ = 137 Hz, c), 24.83 (g or g'), 24.70 (g or g'), 22.34 (d, $^{3}J_{C\text{-}P}$ = 4.0 Hz, e), 20.98 (l), 16.54 (d, $^{3}J_{C\text{-}P}$ = 5.5 Hz, a or a'), 16.49 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.25 (br s) ppm; ^{31}P NMR (162

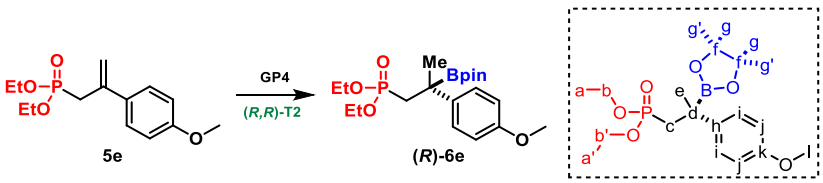
MHz, $CDCl_3$) δ 31.75 ppm; IR (neat) 2977 (aromatic C-H), 2906 (aliphatic C-H), 1511, 1463 (aromatic C=C), 1345, 1240 (P=O), 1153, 1054, 1025 (C-O), 955 (P-O), 836, 729 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the tertiary alcohol **18b**.



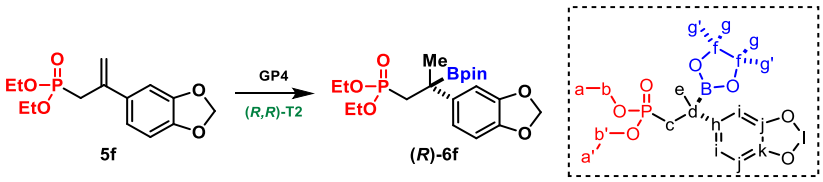
Synthesis of chiral tertiary benzylic boronic ester (*R*)-6c: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5c** (64 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6c** (69 mg, 77%) as a colorless liquid: TLC analysis (ethyl acetate/hexanes 1:3) R_f = 0.5; $[\alpha]_D^{20}$ = -5.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (4H, dd, *J* = 12.5, 9.0 Hz, i+j), 4.06-3.86 (4H, m, b+b'), 2.41 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.20 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.60 (3H, s, e), 1.25-1.18 (18H, m, a+a'+g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.46 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, h), 127.96 (q, $^2J_{C\text{-}F}$ = 32.0 Hz, k), 127.25 (i), 125.11 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, j), 124.55 (q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 84.22 (f), 61.41 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.07 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 35.49 (d, $^1J_{C\text{-}P}$ = 139 Hz, c), 22.24 (g or g'), 22.19 (g or g'), 22.21 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, e), 16.49 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.43 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.28 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.66 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.37 ppm; IR (neat) 2979 (aromatic C-H), 2932 (aliphatic C-H), 1616, 1469 (aromatic C=C), 1381 (aromatic C=C), 1324 (C-F), 1240 (P=O), 1120, 1053 (C-O), 1025 (C-O), 955 (P-O), 844, 831, 679 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18c**.



Synthesis of chiral tertiary benzylic boronic ester (*R*)-6d: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5d** (57 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6d** (63 mg, 76%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = -18° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (2H, t, *J* = 8.0 Hz, l), 7.00 (1H, s, i), 6.97-6.86 (1H, m, m), 6.72 (1H, dd, *J* = 6.5, 2.0 Hz, k), 4.09-3.95 (4H, m, b+b'), 3.80 (3H, d, *J* = 2.0 Hz, n), 2.47 (1H, dd, *J* = 18.0., 15.0 Hz, c(1H)), 2.15 (1H, dd, *J* = 17.5, 15.0 Hz, c(1H)), 1.56 (3H, s, e), 1.31-1.23 (18H, m, a+a'+g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.60 (j), 148.20 (d, $^3J_{C\text{-}P}$ = 16.0 Hz, h), 129.13 (l), 119.08 (i), 112.74 (m), 110.93 (k), 83.90 (f), 41.42 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.04 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 55.33 (n), 35.56 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 24.94 (g or g'), 24.80 (g or g'), 22.38 (d, $^3J_{C\text{-}P}$ = 4.0 Hz, e), 16.62 (d, $^3J_{C\text{-}P}$ = 5.5 Hz, a or a'), 16.57 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.8 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.55 ppm; IR (neat) 2977 (aromatic C-H), 2933 (aliphatic C-H), 1599, 1580, 1486 (aromatic C=C), 1464 (aromatic C=C), 1240 (P=O), 1143, 1024 (C-O), 955 (P-O) cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18d**.

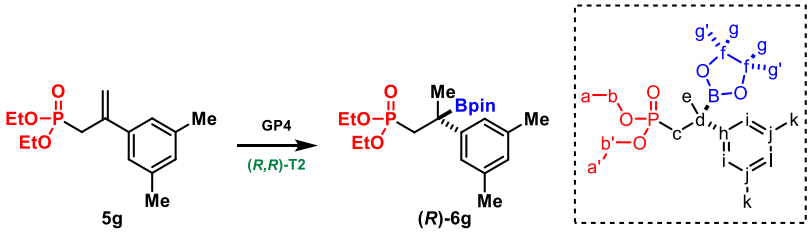


Synthesis of chiral tertiary benzylic boronic ester (*R*)-6e: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5e** (57 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6e** (58 mg, 70%) as a dense waxy liquid: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; $[\alpha]_D^{20}$ = +4.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 9.0 Hz, i), 6.83 (2H, d, *J* = 9.0 Hz, j), 4.08-3.90 (4H, m, b+b'), 3.78 (3H, s, l), 2.43 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.12 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.55 (3H, s, e), 1.29-1.21 (18H, m, a+a'+g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.55 (k), 138.32 (d, $^3J_{C\text{-}P}$ = 16.0 Hz, h), 127.71 (i), 113.71 (j), 83.92 (f), 61.35 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.02 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 55.40 (l), 35.73 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 24.89 (g or g'), 24.76 (g or g'), 22.50 (e), 16.53 (d, $^3J_{C\text{-}P}$ = 4.5 Hz, a or a'), 16.58 (d, $^3J_{C\text{-}P}$ = 4.5 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.0 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.65 ppm; IR (neat) 2976 (aromatic C-H), 2906 (aliphatic C-H), 1607, 1510, 1463 (aromatic C=C), 1242 (P=O), 1142, 1024 (C-O), 954 (P-O) cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18e**.



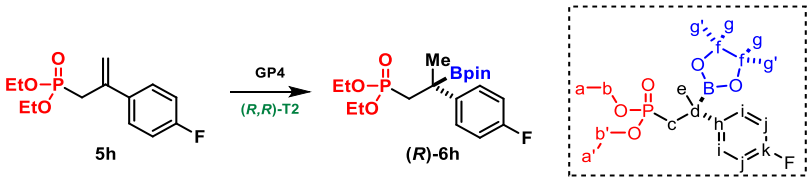
Synthesis of chiral tertiary benzylic boronic ester (*R*)-6f: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5f** (60 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6f** (66 mg, 77%) as a colorless liquid (*Note: This boronic ester was air sensitive. After purification, this product was stored under nitrogen in the freezer)*: TLC analysis (ethyl acetate) R_f = 0.5;

$[\alpha]_D^{20}$ = -7.1° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (1H, d, *J* = 2.0 Hz, i), 6.83 (1H, dd, *J* = 8.0, 2.0 Hz, i), 6.73 (1H, d, *J* = 8.0 Hz, j), 5.90 (2H, s, l), 4.06-3.93 (4H, m, b+b'), 2.38 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.09 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.52 (3H, s, e), 1.29-1.21 (18H, m, a+a'+g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.65 (j or k), 145.45 (j or k), 140.33 (d, $^3J_{C-P}$ = 16.0 Hz, h), 119.57 (i), 108.00 (j), 107.62 (i), 100.89 (l), 83.95 (f), 61.33 (d, $^2J_{C-P}$ = 6.0 Hz, b or b'), 60.98 (d, $^2J_{C-P}$ = 6.0 Hz, b or b'), 35.38 (d, $^1J_{C-P}$ = 138 Hz, c), 24.85 (g or g'), 24.70 (g or g'), 22.57 (d, $^3J_{C-P}$ = 4.5 Hz, e), 16.56 (d, $^3J_{C-P}$ = 5.0 Hz, a or a'), 16.49 (d, $^3J_{C-P}$ = 5.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.1 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.34 ppm; IR (neat) 2977 (aromatic C-H), 2906 (aliphatic C-H), 1487 (aromatic C=C), 1321, 1234 (P=O), 1142, 1024 (C-O), 956 (P-O), 936, 729 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18f**.



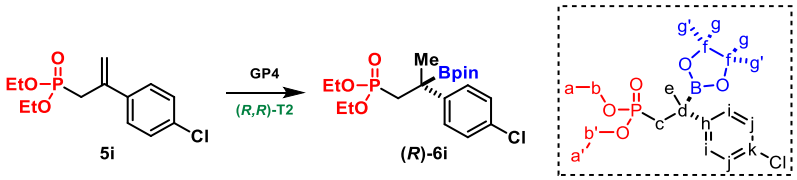
Synthesis of chiral tertiary benzylic boronic ester (*R*)-6g: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5g** (56 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6g** (62 mg, 76%) as a colorless liquid: TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = -4.3° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (2H, s, i), 6.80 (1H, s, l), 4.11-3.92 (4H, m, b+b'), 2.46 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.29 (6H, s, k), 2.12 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.56 (3H, s, e), 1.30 (3H, t, *J* = 7.0, a or a'), 1.25 (3H, t, *J* = 7.0, a or a'), 1.22 (12H,

s, g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.32 (d, $^{3}J_{C\text{-}P}$ = 17 Hz, h), 137.53 (j), 127.33 (l), 124.41 (i), 83.86 (f), 61.32 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 60.91 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 35.39 (d, $^{1}J_{C\text{-}P}$ = 137 Hz, c), 24.86 (g or g'), 24.67 (g or g'), 22.45 (d, $^{3}J_{C\text{-}P}$ = 3.5 Hz, e), 21.63 (k), 16.58 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.52 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.30 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.90 ppm; IR (neat) 2976 (aromatic C-H), 2915 (aliphatic C-H), 1598, 1461 (aromatic C=C), 1321 (aromatic C=C), 1240 (P=O), 1164, 1053 (C-O), 1025 (C-O), 954 (P-O), 839, 697 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18g**.



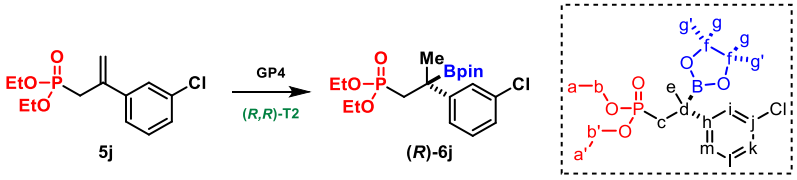
Synthesis of chiral tertiary benzylic boronic ester (*R*)-6h: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5h** (54 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6h** (51 mg, 62%) as a colorless liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = -5.8° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, dd, *J* = 8.5, 5.5 Hz, i), 6.96 (2H, t, *J* = 8.5 Hz, j), 4.06-3.88 (4H, m, b+b'), 2.39 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.14 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.56 (3H, s, e), 1.27-1.20 (18H, m, a+a'+g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.15 (d, $^{1}J_{C\text{-}F}$ = 244 Hz, k), 141.78 (dd, $^{4}J_{C\text{-}F}$ = 3.0 Hz, $^{3}J_{C\text{-}P}$ = 15.0 Hz, h), 128.28 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, i), 114.89 (d, $^{2}J_{C\text{-}F}$ = 21 Hz, j), 84.01 (f), 61.32 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 60.99 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 35.76 (d, $^{1}J_{C\text{-}P}$ = 138 Hz, c), 24.80 (g or g'), 24.68 (g or g'), 22.46 (d, $^{3}J_{C\text{-}P}$ = 5.0 Hz, e), 16.55 (d, $^{3}J_{C\text{-}P}$ = 4.5 Hz, a or a'), 16.49 (d, $^{3}J_{C\text{-}P}$ = 5.0

Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.00 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.12 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.33 ppm; IR (neat) 2977 (aromatic C-H), 2932 (aliphatic C-H), 1603, 1508 (C-F), 1469 (aromatic C=C), 1343 (aromatic C=C), 1323 (aromatic C=C), 1237 (P=O), 1143, 1053 (C-O), 1024 (C-O), 955 (P-O), 838 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18h**.

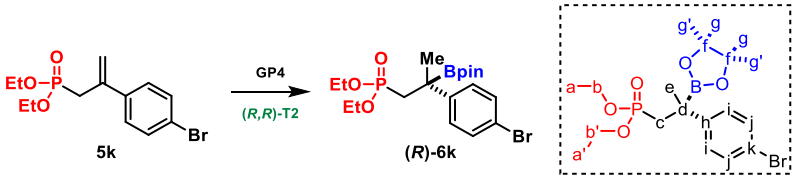


Synthesis of chiral tertiary benzylic boronic ester (*R*)-6i: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5i** (58 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6i** (68 mg, 82%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = -8.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.5 Hz, i or j), 7.24 (2H, d, *J* = 8.5 Hz, i or j), 4.06-3.88 (4H, m, b+b'), 2.38 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.13 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.55 (3H, s, e), 1.27-1.19 (18H, m, a+a'+g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.75 (d, $^3J_{C\text{-}P}$ = 15 Hz, h), 131.44 (k), 128.28 (i or j), 128.24 (i or j), 84.06 (f), 61.36 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.02 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 35.52 (d, $^1J_{C\text{-}P}$ = 139 Hz, c), 24.80 (g or g'), 24.68 (g or g'), 22.24 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, e), 16.54 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, a or a'), 16.48 (d, $^3J_{C\text{-}P}$ = 5.5 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.13 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.99 ppm; IR (neat) 2977 (aromatic C-H), 2931 (aliphatic C-H), 1740, 1492 (aromatic C=C), 1323 (aromatic C=C), 1240

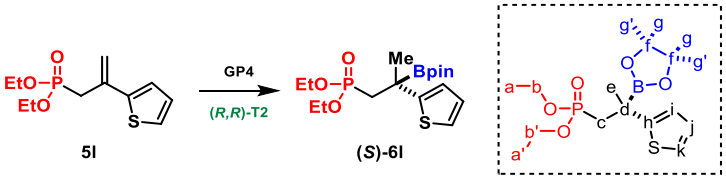
(P=O), 1143, 1053 (C-O), 1024 (C-O), 954 (P-O), 830 (C-Cl) cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18i**.



Synthesis of chiral tertiary benzylic boronic ester (*R*)-6j: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5j** (58 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6j** (53 mg, 64%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 2:5) R_f = 0.5; $[\alpha]_D^{20}$ = -12.4° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, s, i), 7.27 (1H, d, *J* = 8.0 Hz, m or k), 7.20 (1H, t, *J* = 8.0 Hz, l), 7.12 (1H, d, *J* = 8.0 Hz, m or k), 4.07-3.89 (4H, m, b+b'), 2.39 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.13 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.55 (3H, s, e), 1.27-1.20 (18H, m, a+a'+g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.49 (d, $^3J_{C\text{-}P}$ = 15 Hz, h), 134.17 (j), 129.43 (l), 127.06 (i), 125.82 (m or k), 125.06 (m or k), 84.11 (f), 61.39 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.00 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 35.40 (d, $^1J_{C\text{-}P}$ = 139 Hz, c), 24.79 (g or g'), 24.65 (g or g'), 22.16 (d, $^3J_{C\text{-}P}$ = 4.0 Hz, e), 16.53 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, a or a'), 16.47 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.19 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.99 ppm; IR (neat) 2977 (aromatic C-H), 2931 (aliphatic C-H), 1593, 1567, 1472 (aromatic C=C), 1323 (aromatic C=C), 1240 (P=O), 1143, 1053 (C-O), 1024 (C-O), 955 (P-O), 833 (C-Cl) cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18j**.

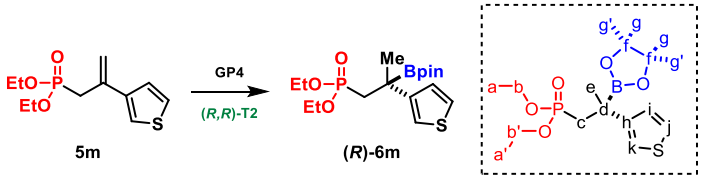


Synthesis of chiral tertiary benzylic boronic ester (*R*)-6k: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5k** (67 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6k** (63 mg, 68%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = -5.2° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.6 Hz, i or j), 7.27 (2H, d, *J* = 8.6 Hz, i or j), 4.07-3.89 (4H, m, b+b'), 2.39 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.14 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.55 (3H, s, e), 1.28-1.20 (18H, m, a+a'+g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.32 (d, $^3J_{C\text{-}P}$ = 15 Hz, h), 131.25 (i or j), 128.68 (i or j), 119.59 (k), 84.10 (f), 61.40 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.06 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 35.74 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 24.83 (g or g'), 24.71 (g or g'), 22.19 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, e), 16.56 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, a or a'), 16.51 (d, $^3J_{C\text{-}P}$ = 5.5 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.05 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.96 ppm; IR (neat) 2977 (aromatic C-H), 2930 (aliphatic C-H), 1488 (aromatic C=C), 1371 (aromatic C=C), 1240 (P=O), 1142, 1053 (C-O), 1023 (C-O), 955 (P-O), 830, 686 (C-Br) cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18k**.



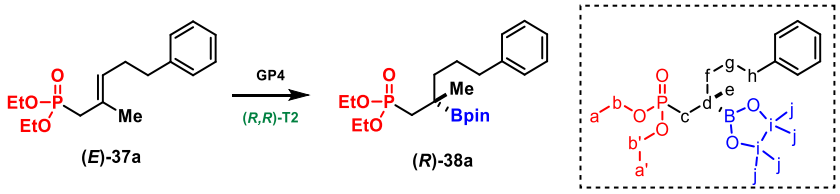
Synthesis of chiral tertiary benzylic boronic ester (*S*)-6l: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5l**

(52 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*S*)-**6l** (66 mg, 85%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = +6.5° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.12-7.11 (1H, m, k), 6.92-6.90 (2H, m, i+j), 4.09-3.98 (4H, m, b+b'), 2.51 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.15 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.62 (3H, s, e), 1.31-1.23 (18H, m, a+a'+g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.35 (d, $^3J_{C-P}$ = 20 Hz, h), 126.78 (i or j), 123.24 (i or j), 122.97 (k), 84.19 (f), 61.53 (d, $^2J_{C-P}$ = 6.0 Hz, b or b'), 61.10 (d, $^2J_{C-P}$ = 7.0 Hz, b or b'), 37.03 (d, $^1J_{C-P}$ = 138 Hz, c), 24.83 (g or g'), 24.76 (g or g'), 24.17 (d, $^3J_{C-P}$ = 5.0 Hz, e), 16.57 (d, $^3J_{C-P}$ = 6.5 Hz, a+a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.78 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.16 ppm; IR (neat) 2978 (aromatic C-H), 2931 (aliphatic C-H), 1739, 1463 (aromatic C=C), 1325 (aromatic C=C), 1236 (P=O), 1142, 1052 (C-O), 1023 (C-O/C=S), 955 (P-O), 731, 692 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18l**.



Synthesis of chiral tertiary benzylic boronic ester (*R*)-6m: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **5m** (52 mg, 0.2 mmol) yields the tertiary benzylic boronic ester product (*R*)-**6m** (62 mg, 80%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = -6.4° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, dd, *J* = 5.0, 3.0 Hz, j), 7.10 (1H, dd, *J* = 5.0, 1.3 Hz, i), 7.03 (1H, dd, *J* = 3.0, 1.3 Hz, k), 4.11-3.94 (4H, m, b+b'), 2.45 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.10 (1H, dd, *J* = 18.0, 15.0 Hz, c), 1.55 (3H, s, e), 1.30-1.24

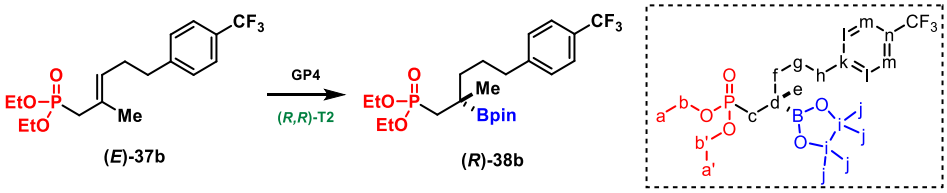
(6H, m, a+a'), 1.20 (12H, s, g+g') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.64 (d, $^{3}J_{C\text{-}P}$ = 17.5 Hz, h), 127.28 (i), 125.00 (j), 119.11 (k), 83.97 (f), 61.39 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.06 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 35.64 (d, $^{1}J_{C\text{-}P}$ = 138 Hz, c), 24.82 (g or g'), 24.74 (g or g'), 22.84 (d, $^{3}J_{C\text{-}P}$ = 5.0 Hz, e), 16.58 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.56 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.29 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.08 ppm; IR (neat) 2977 (aromatic C-H), 2931 (aliphatic C-H), 1739, 1462 (aromatic C=C), 1339 (aromatic C=C), 1320 (C=C), 1239 (P=O), 1143, 1053 (C-O), 1024 (C-O/C=S), 954 (P-O), 776 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **18m**.



Synthesis of chiral tertiary boronic ester (*R*)-38a: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate **37a** (1.18 g, 4.00 mmol) yields the tertiary boronic ester product (*R*)-**38a** (1.39 g, 82%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 3:7) R_f = 0.5; $[\alpha]_D^{20}$ = +6.91° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.15 (5H, m, aryl), 4.11-4.00 (4H, m, b+b'), 2.59 (2H, t, *J* = 7.5 Hz, h). 2.05-1.39 (6H, m, c+f+g), 1.33-1.24 (18H, a+a'+j), 1.11 (3H, s, e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.66 (aryl), 128.35 (aryl), 128.23 (aryl), 125.60 (aryl), 83.40 (i), 61.06-60.78 (m, b+b'), 39.73 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, f), 36.67 (d), 36.67 (h), 34.05 (d, $^{1}J_{C\text{-}P}$ = 136.5 Hz, c), 27.34 (g), 24.89 (j), 22.03 (d, $^{3}J_{C\text{-}P}$ = 6.75 Hz, e), 16.53-16.43 (m, a+a') ppm; ^{31}P NMR (121 MHz) δ 32.35 ppm; ^{11}B NMR (96 MHz) δ 34.65 ppm; IR (neat) 3025.66 (sp^2 C-H), 2977.90 (sp^3 C-H), 1739.56, 1603.55, 1371.34, 1240.12 (P=O),

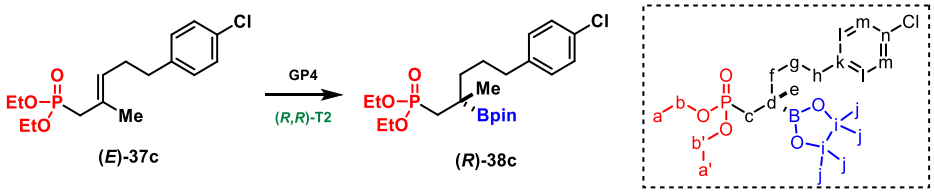
1053.39 (C-O), 1026.23 (C-O), 953.50, 733.60 cm^{-1}; HRMS (ESI) calculated for $C_{22}H_{38}BO_5P$ 424.2550, found 424.2566 *m/z*. The enantiomer ratio was determined by chiral HPLC analysis after oxidation to the tertiary alcohol **40a**. [Note: The isomeric substrate (*Z*)-**37a** reacted under identical conditions to afford *ca*. 40% of the chiral tertiary boronic ester (*R*)-**38a** with an enantiomer ratio of 99:1 and majority of the remaining mixture was the reduced side product.]

Note: Absolute configuration assignment. The stereochemical identity of bakuchiol methyl ether derived from the sequence starting with the boronic ester **38q** generated via CAHB of **37q** using (*S*,*S*)-**T2** was found to be (*S*) by comparison of the optical rotation value with the literature data.[12] Therefore, the absolute configuration of the tertiary boronic ester **38q** formed from CAHB of trisubstituted alkene **37q** using (*S*,*S*)-**T2** is assigned to be *"S"*. Similarly, the enantiomeric (*R*)-(-)-bakuchiol methyl ether was obtained in the sequence starting with the boronic ester **38q** generated via CAHB of **37q** using (*R*,*R*)-**T2**. The absolute configurations of all other tertiary boronic esters generated via CAHB using (*R*,*R*)-**T2**, which was used for most of the examples reported in this dissertation, are hence assigned as *"R"* by analogy.



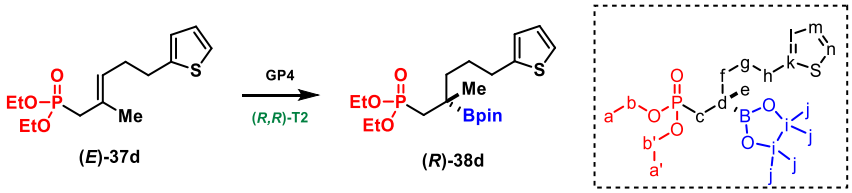
Synthesis of the tertiary boronic ester (*R*)-38b: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene **37b** (91 mg, 0.25 mmol) yields tertiary boronic ester (*R*)-**38b** (96 mg, 78%) as a viscous light buff colored oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ =

+1.5° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* = 8 Hz, m), 7.28 (2H, d, *J* = 8 Hz, l), 4.10-4.01 (4H, m, b+b'), 2.66 (2H, t, *J* = 7.4 Hz, h), 1.95 (1H, dd, *J* = 18, 15.4 Hz, c), 1.74 (1H, dd, *J* = 18, 15.4 Hz, c), 1.66-1.44 (4H, m, f+g), 1.25 (3H, s, e), 1.33-1.29 (6H, m, a+a'), 1.25 (12H, s, j), 1.12 (3H, s, e) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.88 (k), 128.78 (aryl), 128.29 (aryl), 127.97 (CF_3), 125.32 (aryl), 125.28 (aryl), 125.25 (aryl), 83.56 (i), 61.17-60.95 (m, b+b'), 39.40 (d, $^3J_{C\text{-}P}$ = 13 Hz, f), 36.53 (h), 34.09 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 27.14 (g), 24.96 (j), 22.22 (d, $^3J_{C\text{-}P}$ = 7 Hz, e), 16.56 (dd, $^3J_{C\text{-}P}$ = 4 Hz, a+a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 35.59 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.12 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.29 ppm; IR (neat) 2978 (aromatic C-H), 2917 (aliphatic C-H), 1618, 1466, 1323 (C-F), 1241 (P=O), 1119 (C-O), 1026 (C-O), 953 (P-O) cm^{-1}; Enantiomer ratio was determined by chiral HPLC analysis of the tertiary alcohol derivative **40b.**

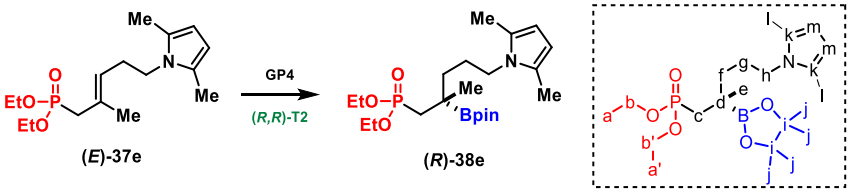


Synthesis of the tertiary boronic ester (*R*)-38c: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (*E*)-**37c** (83 mg, 0.25 mmol) yields tertiary boronic ester (*R*)-**38c** (87 mg, 76%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +2.0° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.22 (2H, m, m), 7.11-7.08 (2H, m, l), 4.10-4.03 (4H, m, b+b'), 2.56 (2H, t, *J* = 7.2 Hz, h), 1.99-1.91 (1H, m, c), 1.76-1.68 (1H, m, c), 1.64-1.39 (4H, m, f+g), 1.33-1.11 (18H, m, a+a'+j), 1.11 (3H, s, e) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.18 (k), 131.39 (n), 129.82 (l), 128.46 (m), 83.54 (i), 61.18-60.94

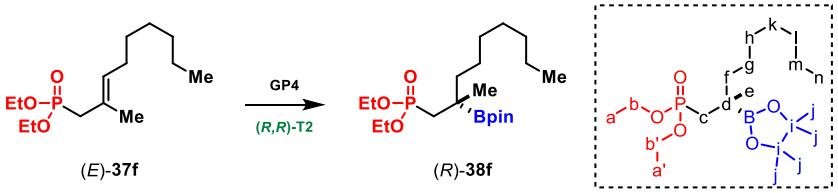
(m, b+b'), 39.52 (d, $^{3}J_{C\text{-}P}$ = 14 Hz, f), 3604 (h), 34.13 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 27.32 (g), 25.00 (j), 22.17 (d, $^{3}J_{C\text{-}P}$ = 7 Hz, e), 16.63-16.55 (m, a+a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 36.17 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.22 ppm; IR (neat) 2977 (aromatic C-H), 2933 (aliphatic C-H), 1492, 1406, 1316, 1241, 1144, 1054, 1026, 953 cm^{-1}; Enantiomer ratio was determined by chiral HPLC analysis of the tertiary alcohol derivative **40c.**



Synthesis of the tertiary boronic ester (*R*)-38d: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (*E*)-**37d** (76 mg, 0.25 mmol) yields tertiary boronic ester (*R*)-**38d** (83 mg, 78%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +1.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (1H, dd, *J* = 6.8, 1.6 Hz, n), 6.91 (1H, dd, *J* = 6.8, 4.8 Hz, m), 6.78-6.77 (1H, m, l), 4.12-4.03 (4H, m, b+b'), 2.81 (2H, t, *J* = 7.2 Hz, h), 2.03-1.92 (1H, m, c), 1.79-1.45 (5H, m, c+f+g), 1.34-1.27 (18H, m, a+a'+j), 1.13 (3H, s, e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.61 (k), 126.63 (m), 123.93 (l), 122.76 (n), 83.47 (i), 61.09-60.83 (m, b+b'), 39.50 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, f), 34.07 (d, $^{1}J_{C\text{-}P}$ = 136.5 Hz, c), 30.63 (h), 27.77 (g), 24.91 (j), 22.06 (d, $^{3}J_{C\text{-}P}$ = 7.5 Hz, e), 16.54-16.43 (m, a+a') ppm; ^{11}B NMR (96 MHz, $CDCl_3$) δ 36.18 ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 32.24 ppm; IR (neat) 2978 (C-H), 2165, 2027, 1739, 1465, 1371, 1215 (P=O), 1142 (C-O), 1026 (C-O/C-B), 961 (P-O) cm^{-1}; Enantiomer ratio was determined by chiral HPLC analysis of the tertiary alcohol derivative **40d.**

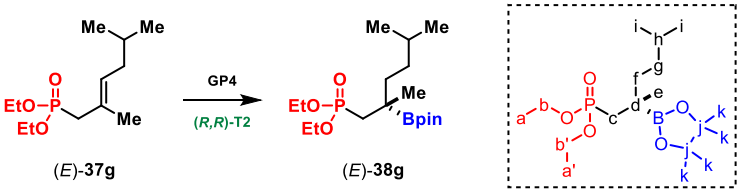


Synthesis of the tertiary boronic ester (*R*)-38e: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (*E*)-**37e** (78 mg, 0.25 mmol) yielded tertiary boronic ester (*R*)-**38e** (79 mg, 71%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +1.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (2H, s, m), 4.14-4.04 (4H, m, b+b'), 3.70 (2H, t, *J* = 7.5 Hz, h), 2.23 (6H, s, l), 1.98-1.72 (2H, m, c), 1.69-1.43 (4H, m, g+h), 1.36-1.26 (18H, m, a+a'+j), 1.12 (3H, s, e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.21 (k), 104.92 (m), 83.51 (i), 61.03 (dd, $^2J_{C\text{-}P}$ = 6 Hz, b+b'), 44.23 (h), 36.13 (d, $^3J_{C\text{-}P}$ = 12 Hz, f), 33.72 (d, $^1J_{C\text{-}P}$ = 136.5 Hz, c), 27.14 (g), 24.88 (j), 22.31 (d, $^3J_{C\text{-}P}$ = 9 Hz, e), 16.50 (d, $^3J_{C\text{-}P}$ = 5.25 Hz, a+a'), 12.43 (l) ppm; ^{11}B NMR (96 MHz, $CDCl_3$) δ 35.59 ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 31.96 ppm; IR (neat) 2976 (sp^2 C-H), 2932 (sp^3 C-H), 1371 (C=N/B-O), 1299, 1245 (P=O), 1052 (C-O), 1025 (C-O), 955 (P-O), 741 cm^{-1}; Enantiomer ratio was determined by chiral HPLC analysis of the tertiary alcohol derivative **40e.**



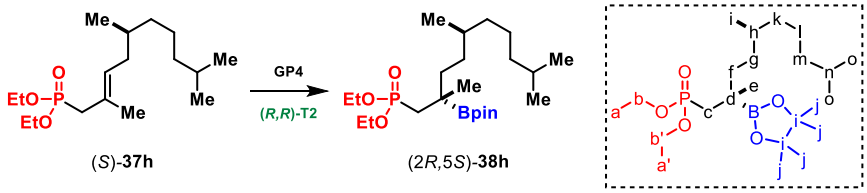
Synthesis of the tertiary boronic ester (*R*)-38f: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (*E*)-**37f** (69 mg, 0.25 mmol) yields tertiary boronic ester (*R*)-**38f** (84 mg, 83%) as a

colorless oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.7; $[\alpha]_D^{20}$ = +1.1° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.12-4.00 (4H, m, b+b'), 2.03-1.94 (1H, m, c), 1.75-1.67 (1H, m, c), 1.50-1.42 (2H, m, m), 1.36-1.27 (28H, a+a'+f+g+h+j+k+l), 1.12 (3H, s, e), 0.89 (3H, t, *J* = 7.0 Hz, n) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.46 (i), 61.14-60.86 (m, b+b'), 40.40 (d, $^3J_{C-P}$ = 16 Hz, f), 34.28 (d, $^1J_{C-P}$ = 136 Hz, c), 31.95, 30.44, 29.36, 25.37, 25.01 (j), 22.75 (m), 22.04 (d, $^3J_{C-P}$ = 6 Hz, e),, 16.60-16.54 (m, a+a'), 14.21 (n) ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 35.14 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.56 ppm; IR (neat) 2976 (C-H), 1467, 1371 (B-O), 1241 (P=O), 1144, 1055, 1027 (C-O), 953 (P-O) cm^{-1}; Enantiomer ratio was determined by NMR analysis of the γ-amino-phosphonate derivative **79f.**

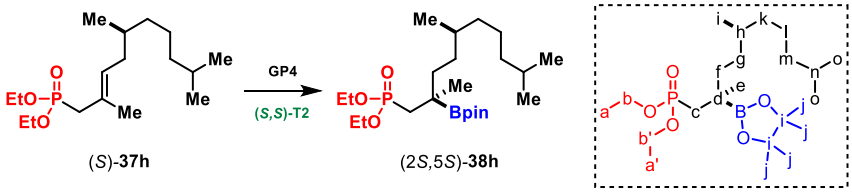


Synthesis of the tertiary boronic ester (*R*)-38g: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (*E*)-**37g** (62 mg, 0.25 mmol) yielded tertiary boronic ester (*R*)-**38g** (76 mg, 80%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 3:7) R_f = 0.5; $[\alpha]_D^{20}$ = +0.9° (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.10-4.00 (4H, m, b+b'), 1.97 (1H, dd, *J* = 18, 15.5 Hz, c), 1.68 (1H, dd, *J* = 18, 15.5 Hz, c), 1.49-1.36 (3H, m, h+ f or g), 1.33-1.23 (18H, m, a+a'+k), 1.19-1.13 (2H, m, f or g), 1.095 (3H, s, e), 0.86 (6H, d, *J* = 6.6 Hz, i) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.55 (j), 61.05-60.71 (m, b+b'), 38.17 (d, $^3J_{C-P}$ = 15.75 Hz, f), 34.23 (d, $^1J_{C-P}$ = 135.75 Hz, c), 34.42 (d, $^4J_{C-P}$ = 1.5 Hz, g), 28.74 (h), 24.90 (k), 22.66 (i), 21.83 (d, $^3J_{C-P}$ = 6 Hz, e), 16.50-16.41 (m, a+a') ppm; ^{11}B NMR (96 MHz) δ 34.01 ppm;

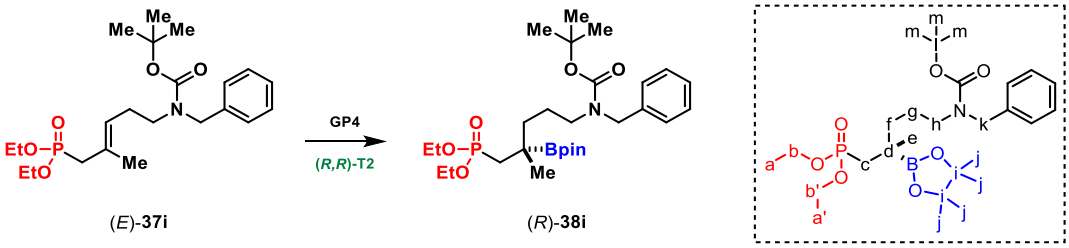
^{31}P NMR (121 MHz) δ 32.55 ppm; IR (neat) 2976 (C-H), 1468, 1241 (P=O), 1054 (C-O), 1026.20 (C-O), 953, 686 cm^{-1}; The enantiomer ratio was determined by chiral HPLC analysis of the furan coupled derivative **73g.**



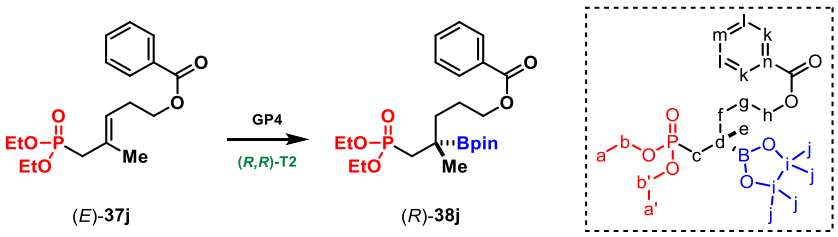
Synthesis of the tertiary boronic ester (2*R*,5*S*)-**38h:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized chiral substrate (*S*)-**37h** (80 mg, 0.25 mmol) yields diastereomeric tertiary boronic ester (2*R*,5*S*)-**38h** (93 mg, 83%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 3:7) R_f = 0.5; $[\alpha]_D^{20}$ = +3.75° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10-4.01 (4H, m, b+b'), 2.01-1.91 (1H, m, c), 1.73-1.61 (1H, m, c), 1.54-1.07 (33H, m, a+a'+e+f+g+h+j+k +l+m+n), 0.87-0.83 (9H, m, i+o) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.60 (i), 61.24-60.96 (m, b+b'), 39.65, 38.17 (d, $^3J_{C\text{-}P}$ = 15 Hz, f), 37.62, 34.81 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 33.86, 32.86, 28.22, 25.21 (j), 25.19, 22.87, 22.78, 22.15 (d, $^3J_{C\text{-}P}$ = 5 Hz, e), 19.97, 16.67 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{11}B NMR (128 MHz) δ 35.80 ppm; ^{31}P NMR (162 MHz) δ 32.36 ppm; IR (neat) 2927 (C-H), 1466, 1371, 1315, 1242 (P=O), 1145 (B-O), 1055 (C-O), 1027 (C-O), 953 (C-O) cm^{-1}; HRMS (ESI) calculated for $C_{23}H_{48}BO_5P$+Na^+ 468.3266, found 468.3268 *m/z*. Diastereomer ratio (dr) estimate = >20:1. The dr was estimated from ^{13}C NMR analysis of the sample by comparison with the ^{13}C NMR spectrum of its diastereomer (2*S*,5*S*)-**38h**.



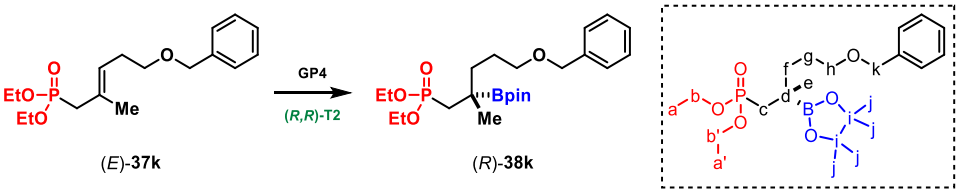
Synthesis of the tertiary boronic ester (2*S*,5*S*)-**38h:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*S*,*S*)-**T2**, the phosphonate functionalized chiral substrate (*S*)-**37h** (80 mg, 0.25 mmol) yields diastereomeric tertiary boronic ester (2*S*,5*S*)-**38h** (92 mg, 82%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 3:7) R_f = 0.5; $[\alpha]_D^{20}$ = –3.25° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10-4.02 (4H, m, b+b'), 2.03-1.94 (1H, m, c), 1.73-1.65 (1H, m, c), 1.58-1.06 (33H, m, a+a'+e+f+g+h+j+k+l+m+n), 0.88-0.85 (9H, m, i+o) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.62 (i), 61.25-60.97 (m, b+b'), 39.66, 38.15 (d, $^3J_{C\text{-}P}$ = 15 Hz, f), 37.62, 34.66 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 33.88, 32.89, 28.23, 25.20 (j), 25.04, 22.88, 22.80, 22.25 (d, $^3J_{C\text{-}P}$ = 6 Hz, e), 19.98, 16.67 (d, $^3J_{C\text{-}P}$ = 4 Hz, a+a') ppm; ^{11}B NMR (128 MHz) δ 34.69 ppm; ^{31}P NMR (162 MHz) δ 32.42 ppm; IR (neat) 2927 (C-H), 1467, 1371, 1315, 1242 (P=O), 1145 (B-O), 1055 (C-O), 1027 (C-O), 953 (C-O) cm^{-1}; HRMS (ESI) calculated for $C_{23}H_{48}BO_5P$+Na^+ 468.3266, found 468.3268 *m/z*. Diastereomer ratio (dr) estimate = >20:1. The dr was estimated from ^{13}C NMR analysis of the sample by comparison with the ^{13}C NMR spectrum of its diastereomer (2*S*,5*S*)-**38h**.



Synthesis of the tertiary boronic ester (*E*)-37i: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R,R*)-**T2**, the phosphonate functionalized alkene (*E*)-**37i** (102 mg, 0.25 mmol) yields tertiary boronic ester (*R*)-**38i** (94 mg, 70%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = +1.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d6, 353K) δ 7.34-7.22 (5H, m, aryl), 4.38 (2H, s, k), 4.01-3.93 (4H, m, b+b'), 3.11 (2H, t, *J* = 7.0 Hz, h), 1.83-1.75 (1H, m, c), 1.64-1.56 (1H, m, c), 1.42 (9H, s, m), 1.47-1.19 (4H, m, f+h), 1.24-1.22 (6H, m, a+a'), 1.20 (12H, s, j), 0.98 (3H, s, e) ppm; ^{13}C NMR (100 MHz, DMSO-d6, 353K) 155.59 (carbamate C=O), 139.40 (aryl), 128.83 (aryl), 127.74 (aryl), 127.42 (aryl), 83.67 (i), 79.26 (l), 61.10-60.94 (m, b+b'), 50.48 (k), 47.80 (h), 37.22 (d, $^3J_{C\text{-}P}$ = 14 Hz, f), 34.44 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 28.69 (m), 25.25 (j), 24.34 (g), 22.51 (d, $^3J_{C\text{-}P}$ = 7 Hz, e), 16.73 (d, $^3J_{C\text{-}P}$ = 5 Hz, a+a') ppm; ^{11}B NMR (128 MHz, DMSO-d6, 353K) 34.84 ppm; ^{31}P NMR (162 MHz, DMSO-d6, 353K) 30.99 ppm; IR (neat) 2976 (aromatic C-H), 2931 (aliphatic C-H), 1691 (carbamate C=O), 1454, 1413, 1365, 1241 (P=O), 1164 (B-O), 1143 (C-O), 1026 (C-O), 954 (P-O) cm^{-1}. The enantiomer ratio was determined by NMR analysis of diastereomer ratio of the derivative **79i.** [*Note: NMR data for this molecule were recorded at a higher temperature (80°C, 353K) to speed up the interconversions between the tertiary amide rotamers at the NMR time scale which resulted in clean spectra. Room temperature NMR shows broadened peaks which results due to slow interconversions between the rotamers.*]

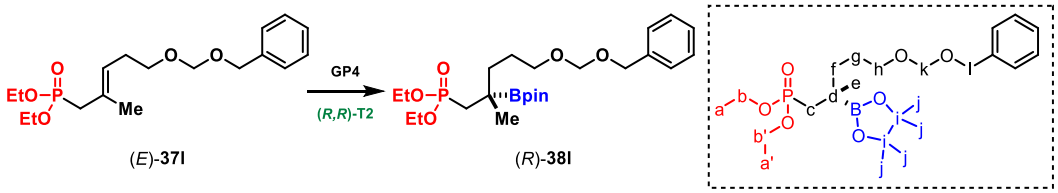


Synthesis of the tertiary boronic ester (*R*)-**38j:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (*E*)-**37j** (85 mg, 0.25 mmol) yields tertiary boronic ester (*R*)-**38j** (75 mg, 64%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = –3.8° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (2H, d, *J* = 7.2 Hz, k), 7.56-7.53 (1H, m, m), 7.45-7.41 (2H, m, l), 4.28 (2H, t, *J* = 6.4 Hz, h), 4.10-4.02 (4H, m, b+b'), 2.02-1.53 (6H, m, c+f+g), 1.32-1.28 (6H, m, a+a'), 1.25 (12H, s, j), 1.14 (3H, s, e) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.70 (C=O), 132.89 (m), 130.59 (n), 129.65 (k), 128.39 (l), 83.64 (i), 65.63 (h), 61.24-61.00 (m, b+b'), 36.01 (d, $^3J_{C\text{-}P}$ = 15 Hz, f), 34.15 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 24.99 (j), 24.92 (g), 22.20 (d, $^3J_{C\text{-}P}$ = 8 Hz, e), 16.58 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 36.12 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.00 ppm; IR (neat) 2976 (aromatic C-H), 2870 (aliphatic C-H), 1717 (C=O), 1452, 1272 (P=O), 1144 (B-O), 1052 (C-O), 1024 (C-O), 954 (P-O) cm^{-1}; Enantiomer ratio was determined by chiral HPLC analysis of the tertiary alcohol derivative **40j.**



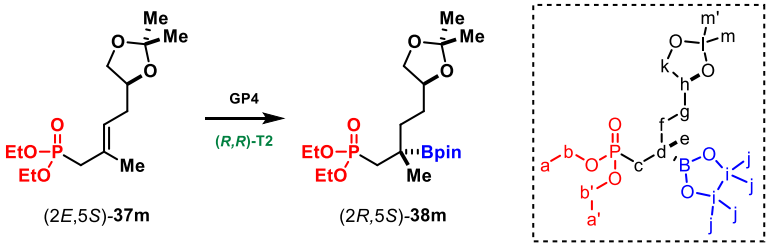
Synthesis of the tertiary boronic ester (*R*)-**38k:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (*E*)-**37k** (79 mg, 0.25 mmol) yields tertiary boronic ester (*R*)-**38k** (89 mg, 78%) as a colorless oil: TLC analysis (ethyl-acetate:hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +2.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.23 (5H, m, aryl), 4.49 (2H, s, k), 4.12-4.00 (4H, m, b+b'), 3.44 (2H, t, *J* = 6.6 Hz, h), 2.02-1.37 (6H, m, c+f+g), 1.32-1.25 (18H, m,

a+a'+j), 1.12 (3H, s, e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.68 (aryl), 128.29 (aryl), 127.58 (aryl), 127.42 (aryl), 83.43 (i), 72.73 (k), 71.02 (h), 61.07-60.81 (m, b+b'), 36.06 (d, $^3J_{C\text{-}P}$ = 15 Hz, f), 34.04 (d, $^1J_{C\text{-}P}$ = 136.5 Hz, c), 25.52 (g), 24.91 (j), 22.03 (d, $^3J_{C\text{-}P}$ = 7.5 Hz, e), 16.46 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{11}B NMR (96 MHz) 33.38 ppm; ^{31}P NMR (121 MHz) 32.24 ppm; IR (neat) 2976 (aromatic C-H), 2866 (aliphatic C-H), 1454, 1370, 1316, 1240 (P=O), 1098 (B-O), 1053 (C-O), 1025 (C-O), 954 (P-O) cm^{-1}; Enantiomer ratio was determined by chiral HPLC analysis of the tertiary alcohol derivative **40k.**

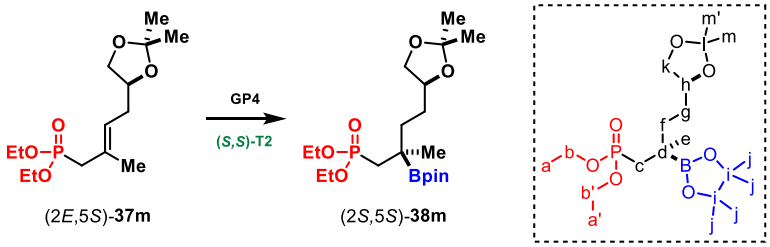


Synthesis of the tertiary boronic ester (*R*)-**38l:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (*E*)-**37l** (89 mg, 0.25 mmol) yields tertiary boronic ester (*R*)-**38l** (98 mg, 81%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +2.2° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.25 (5H, m, aryl), 4.74 (2H, s, l), 4.59 (2H, s, k), 4.13-3.98 (4H, m, b+b'), 3.56 (2H, t, *J* = 6.4 Hz, h), 2.03-1.38 (6H, m, c+f+g), 1.33-1.25 (18H, m, a+a'+j), 1.13 (3H, s, e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.97 (aryl), 128.39 (aryl), 127.86 (aryl), 127.63 (aryl), 94.48 (k), 83.46 (i), 69.20 (l), 68.58 (h), 61.10-60.83 (m, b+b'), 36.22 (d, $^3J_{C\text{-}P}$ = 15 Hz, f), 34.09 (d, $^1J_{C\text{-}P}$ = 137.25 Hz, c), 25.49 (g), 24.91 (j), 22.01 (d, $^3J_{C\text{-}P}$ = 6.75 Hz, e), 16.47 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{11}B NMR (96 MHz) 33.33 ppm; ^{31}P NMR (121 MHz) 32.21 ppm; IR (neat) 2976 (aromatic C-H), 2929 (aliphatic C-H), 1468, 1371, 1316, 1241 (P=O), 1144 (B-O), 1025 (C-O), 953 (P-O) cm^{-1};

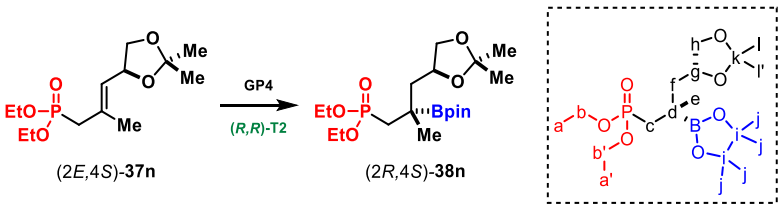
Enantiomer ratio was determined by chiral HPLC analysis of the tertiary alcohol derivative **40l.**



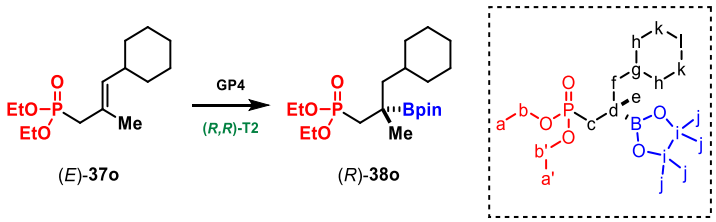
Synthesis of the tertiary boronic ester (2*R*,5*S*)-**38m:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (2*E*,5*S*)-**37m** (77 mg, 0.25 mmol) yielded tertiary boronic ester (2*R*,5*S*)-**4m** (89 mg, 82%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = +1.4° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.10-4.02 (6H, m, b+b'+k/h), 3.53-3.50 (1H, m, k/h), 1.97-1.93 (1H, m, c), 1.76-1.71 (1H, m, c), 1.66-1.60 (2H, m, g), 1.51-1.49 (1H, m, f), 1.40 (3H, s, m or m'), 1.34 (3H, s, m or m'), 1.32-1.30 (6H, m, a+a'), 1.26 (13H, s, j; 1-H of *f* overlaps), 1.11 (3H, s, e) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) 108.58 (l), 83.52 (i), 76.51 (h), 69.46 (k), 61.09-60.92 (m, b+b'), 35.26 (d, $^3J_{C\text{-}P}$ = 14 Hz, f), 33.91 (d, $^1J_{C\text{-}P}$ = 138.25 Hz, c), 29.45 (g), 26.92 (m or m'), 25.71 (m or m'), 24.91 (j), 22.01 (d, $^3J_{C\text{-}P}$ = 8.75 Hz, e), 16.46 (d, $^3J_{C\text{-}P}$ = 5.25 Hz, a+a') ppm; ^{11}B NMR (128 MHz) δ 35.80 ppm; ^{31}P NMR (162 MHz) δ 32.03 ppm; IR (neat) 2978 (C-H), 1466, 1370, 1240 (P=O), 1144 (B-O), 1053 (C-O), 1025 (C-O), 954 (P-O) cm^{-1}; Diastereomer ratio (dr) was determined by ^{31}P-NMR analysis of the tertiary alcohol derivative (2*S*,5*S*)-**38m.**



Synthesis of the tertiary boronic ester (2*S*,5*S*)-**38m:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*S*,*S*)-**T2**, the phosphonate functionalized alkene (2*E*,5*S*)-**37m** (77 mg, 0.25 mmol) yielded tertiary boronic ester (2*S*,5*S*)-**38m** (88 mg, 81%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = +1.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.07-3.99 (6H, m, b+b'+k/h), 3.52-3.50 (1H, m, k/h), 1.95-1.90 (1H, m, c), 1.74-1.67 (1H, m, c), 1.49-1.41 (5H, m, f+g+h), 1.37 (3H, s, m or m'), 1.32 (3H, s, m or m'), 1.30-1.23 (6H, m, a+a'), 1.23 (13H, s, j; 1-H of *f* overlaps), 1.09 (3H, s, e) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) 108.54 (l), 83.49 (i), 76.51 (h), 69.45 (k), 61.07-60.87 (m, b+b'), 35.37 (d, $^3J_{C\text{-}P}$ = 14 Hz, f), 33.72 (d, $^1J_{C\text{-}P}$ = 136.5 Hz, c), 29.65 (g), 26.91 (m or m'), 25.69 (m or m'), 24.88 (j), 22.04 (d, $^3J_{C\text{-}P}$ = 7 Hz, e), 16.47-16.42 (m, a+a') ppm; ^{11}B NMR (128 MHz) 35.80 ppm; ^{31}P NMR (162 MHz) 32.03 ppm; IR (neat) 2980 (C-H), 1467, 1370, 1241 (P=O), 1144 (B-O), 1053 (C-O), 1025 (C-O), 954 (P-O) cm^{-1}; Diastereomer ratio (dr) was determined by ^{31}P-NMR analysis of the tertiary alcohol derivative (2*R*,5*S*)-**38m.**

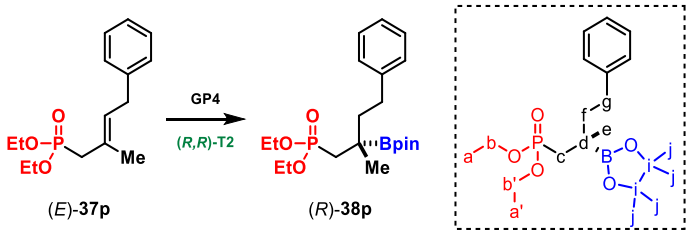


Synthesis of the tertiary boronic ester (2*R*,4*S*)-**38n:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (2*E*,4*S*)-**37n** (74 mg, 0.25 mmol) yields tertiary boronic ester (2*R*,4*S*)-**38n** (54 mg, 51%) as a colorless oil [*Note: A higher catalyst loading (3 mol%) and extended reaction time (24 hours) was needed to force reaction to completion.*]: TLC analysis (7:3 ethyl acetate : hexanes) R_f = 0.5; $[\alpha]_D^{20}$ = +1.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.23-4.20 (1H, m, g or h), 4.12-4.03 (5H, m, b+b' and g or h), 3.45-3.43 (1H, m, g or h), 2.00-1.93 (2H, m, c), 1.82-1.79 (1H, m, f), 1.74-1.71 (1H, m, f), 1.38 (3H, s, l or l'), 1.33 (3H, s, l or l'), 1.33-1.30 (6H, m, a+a'), 1.26 (6H, s, j), 1.25 (6H, s, j), 1.19 (3H, s, e) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 108.79 (k), 83.70 (i), 73.93 (g), 70.50 (h), 61.26-61.06 (m, b+b'), 41.95 (d, $^3J_{C\text{-}P}$ = 10.5 Hz, f), 33.17 (d, $^1J_{C\text{-}P}$ = 136.5 Hz, c), 27.29 (l or l'), 26.25 (l or l'), 25.16 (j), 24.88 (j), 23.25 (d, $^3J_{C\text{-}P}$ = 7 Hz, e), 16.69-16.61 (m, a+a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 35.10 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.29 (Minor diastereomer; 9.4%), 32.11 (Major diastereomer; 90.6%); IR (neat) 2982 (C-H), 1518, 1474, 1371, 1265 (P=O), 1143 (B-O), 1054 (C-O), 1026 (C-O), 965 (P-O), 733 cm^{-1}; HRMS (ESI) calculated for $C_{19}H_{38}BO_7P$+Na^+ 443.2346, found 443.2362 *m/z*.



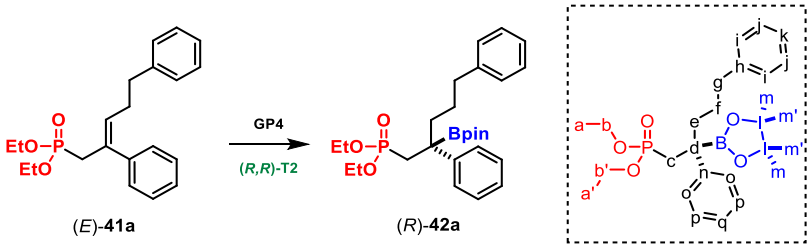
Synthesis of the tertiary boronic ester (*R*)-**38o:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene (*E*)-**37o** (69 mg, 0.25 mmol) yielded tertiary boronic ester (*R*)-**38o** (53 mg, 52%) as

a colorless oil [*Note: A higher catalyst loading (3 mol%) and extended reaction time (24 hours) was needed to force reaction to completion.*]: *TLC* analysis (ethyl-acetate/hexanes 4:6) R_f = 0.5; $[\alpha]_D^{20}$ = +1.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16-4.03 (4H, m, b+b'), 2.05-1.94 (1H, m, c), 1.75-0.91 (35H, m, overlapping a+a'+c(1H)+e+f+g+h+j+k+l) ppm; ^{31}C NMR (75 MHz, $CDCl_3$) δ 83.42 (i), 61.07-60.71 (m, b+b'), 47.71 (d, $^3J_{C\text{-}P}$ = 15 Hz, f), 35.08 (h), 34.43 (d, $^1J_{C\text{-}P}$ = 135.75 Hz, c), 34.93 (g), 26.44 (k), 26.29 (l), 25.03 (j), 24.95 (j), 22.31 (d, $^3J_{C\text{-}P}$ = 4.5 Hz, e), 16.50-16.42 (m, a+a') ppm; ^{11}B NMR (96 MHz, $CDCl_3$) δ 34.32 ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 32.37 ppm; IR (neat) 2921 (C-H), 1488, 1371, 1315, 1242 (P=O), 1142 (B-O), 1054 (C-O), 1026 (C-O), 953 (P-O), 833 cm^{-1}; The enantiomer ratio was determined by chiral HPLC analysis of the furan coupled derivative **73o**.



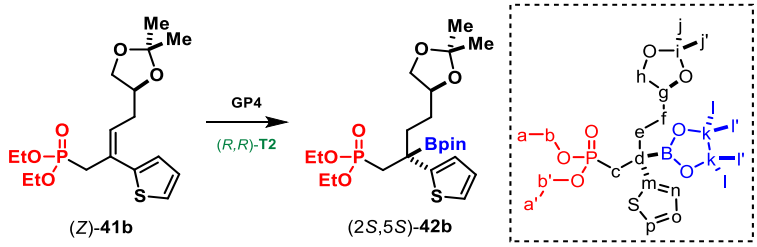
Synthesis of the tertiary boronic ester (*R*)-**38p:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the phosphonate functionalized alkene **37p** (71 mg, 0.25 mmol) yielded tertiary boronic ester (*R*)-**38p** (55 mg, 53%) as a viscous light yellow oil: TLC analysis (ethyl-acetate:hexanes 4:6) R_f = 0.5; $[\alpha]_D^{20}$ = +3.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.14 (5H, m, aryl), 4.15-4.05 (4H, m, b+b'), 2.68-2.53 (2H, m, g), 2.11-2.00 (1H, m, c), 1.86-1.63 (3H, m, c+f), 1.35-1.30 (18H, m, a+a'+j), 1.22 (3H, s, e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.03 (aryl), 128.35 (aryl), 128.28 (aryl), 125.60 (aryl), 83.55 (i), 61.17-60.88 (m, b+b'), 42.32 (d, $^3J_{C\text{-}P}$ = 15

Hz, f), 34.04 (d, $^{1}J_{C\text{-}P}$ = 137.25 Hz, c), 31.90 (g), 24.98 (j), 22.04 (d, $^{3}J_{C\text{-}P}$ = 6.75 Hz, e), 16.50 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{11}B NMR (96 MHz) δ 34.02 ppm; ^{31}P NMR (121 MHz) δ 32.20 ppm; IR (neat) 3025 (aliphatic C-H), 2977 (aliphatic C-H), 2227, 1604, 1371, 1241 (P=O), 1053 (C-O), 1025 (C-O), 954, 730 cm^{-1}; Enantiomer ratio was determined by chiral HPLC analysis of the tertiary alcohol derivative **40p.**



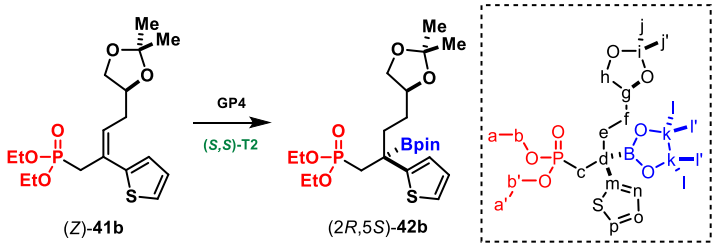
Synthesis of chiral tertiary benzylic boronic ester (*R*)-**42a:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate (*E*)-**41a** (54 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (*R*)-**42a** (60 mg, 82%) as a colorless liquid: TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = +6.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.11 (10H, m, aryl), 4.05-3.84 (4H, m, b+b'), 2.65-2.53 (2H, m, g), 2.40 (2H, d, *J* = 18.0 Hz, c), 2.27-2.12 (2H, m, e), 1.56-1.49 (1H, m, f(1H)), 1.45-1.34 (1H, m, f(1H)), 1.27-1.21 (18H, m, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.33 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, n), 142.91 (h), 128.48 (aryl), 128.29 (aryl), 128.25 (aryl), 127.16 (aryl), 125.65 (aryl), 125.57 (aryl), 83.86 (l), 61.32 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 60.81 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 36.70 (g), 35.14 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, e), 31.11 (d, $^{1}J_{C\text{-}P}$ = 139 Hz, c), 26.58 (f), 24.87 (m or m'), 24.84 (m or m'), 16.58 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.54 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 32.54 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.13; IR (neat) 2983 (aromatic C-H), 2932 (aliphatic C-H), 1618, 1373 (aromatic C=C), 1327 (aromatic C=C), 1239 (P=O), 1055 (C-O), 1024

(C-O), 957 (P-O) cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **43a.**



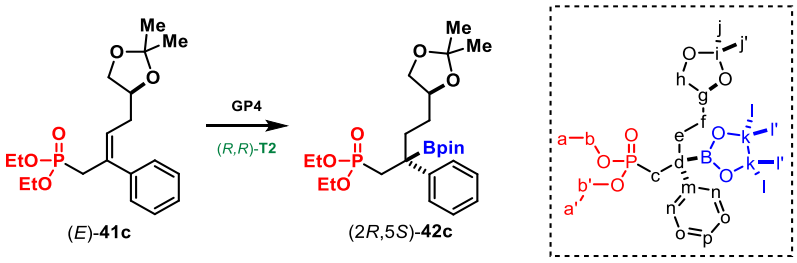
Synthesis of chiral tertiary benzylic boronic ester (2*S*,5*S*)-**42b:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) using (*R*,*R*)-**T2**, the substrate (*Z*)-**41b** (56 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*S*,5*S*)-**42b** (62 mg, 82%) as a colorless viscous liquid. Alternatively, following **GP4** using (*R*,*R*)-**T2**, the diastereomeric substrate (*E*)-**41b** (56 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*S*,5*S*)-**42b** (61 mg, 81%) as a colorless viscous liquid. TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = +2.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (1H, dd, *J* = 5.0, 1.3 Hz, p), 6.93-6.90 (2H, m, n+o), 4.06-3.87 (6H, m, b+b'+g+h(1H)), 3.48-3.43 (1H, m, h(1H)), 2.42 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.34 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.15 (1H, ddd, *J* = 18.0, 13.5, 4.5 Hz, e(1H)), 1.96 (1H, ddd, *J* = 18.0, 13.5, 4.5 Hz, e(1H)), 1.69-1.61 (1H, m, f(1H)), 1.39-1.30 (1H, m, f(1H)), 1.35 (3H, s, j or j'), 1.32 (3H, s, j or j'), 1.29-1.22 (18H, m, a+a'+l+l') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.73 (d, $^3J_{C\text{-}P}$ = 18 Hz, m), 126.76 (n or *o*), 124.41 (n or *o*), 123.30 (p), 108.66 (i), 84.24 (k), 76.55 (g), 69.67 (h), 61.55 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.14 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 33.74 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, e), 33.20 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 28.72 (f), 27.04 (j or j'), 25.84 (j or j'), 24.93 (l or l'), 24.91 (l or l'), 16.56 (d, $^3J_{C\text{-}P}$ = 7.0 Hz, a+a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.01 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.31 ppm; IR (neat)

2979 (aromatic C-H), 2933 (aliphatic C-H), 1369 (aromatic C=C), 1326 (aromatic C=C), 1239 (P=O), 1142, 1052 (C-O), 1024 (C-O/C=S), 956 (P-O), 833, 692 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol (2*R*,5*S*)-**43b**.



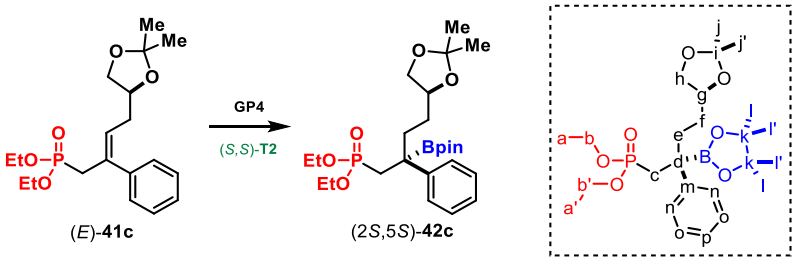
Synthesis of chiral tertiary benzylic boronic ester (2*R*,5*S*)-**42b:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*S*,*S*)-**T2**, the substrate (*Z*)-**41b** (56 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*R*,5*S*)-**42b** (61 mg, 81%) as a colorless viscous liquid. Alternatively, following **GP4** with (*S*,*S*)-**T2**, the diastereomeric substrate (*E*)-**41b** (56 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*R*,5*S*)-**42b** (60 mg, 79%) as a colorless viscous liquid.: TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = +6.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (1H, dd, *J* = 5.0, 1.0 Hz, p), 6.95 (1H, dd, *J* = 3.5, 1.0 Hz, o), 6.91 (1H, dd, *J* = 5.0, 3.5 Hz, n), 4.07-3.86 (6H, m, b+b'+g+h(1H)), 3.52-3.43 (1H, m, h(1H)), 2.42 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.34 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.16 (1H, ddd, *J* = 17.0, 13.0, 4.0 Hz, e(1H)), 1.93 (1H, ddd, *J* = 18.0, 13.5, 4.5 Hz, e(1H)), 1.58-1.41 (2H, m, f), 1.35 (3H, s, j or j'), 1.32 (3H, s, j or j'), 1.30-1.22 (18H, m, a+a'+l+l') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.56 (d, $^3J_{C\text{-}P}$ = 18 Hz, m), 126.78 (n), 124.66 (o), 123.26 (p), 108.67 (i), 84.23 (k), 76.60 (g), 69.59 (h), 61.60 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.11 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 33.89 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, e), 33.44 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 28.86 (f), 27.08 (j or j'), 25.87 (j

or j'), 24.95 (l or l'), 24.88 (l or l'), 16.55 (d, $^{3}J_{C\text{-}P}$ = 7.0 Hz, a+a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 32.59 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.32 ppm; IR (neat) 2978 (aromatic C-H), 2933 (aliphatic C-H), 1369 (aromatic C=C), 1326 (aromatic C=C), 1240 (P=O), 1142, 1051 (C-O), 1024 (C-O/C=S), 959 (P-O), 833, 693 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol (2*S*,5*S*)-**43a**.



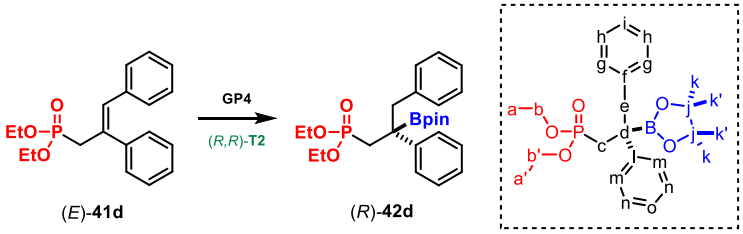
Synthesis of chiral tertiary benzylic boronic ester (2*R*,5*S*)-42c: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate (*E*)-**41c** (55 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*R*,5*S*)-**42c** (60 mg, 80%; 91:9 dr, determined via ^{31}P NMR analysis) as a colorless viscous liquid. Alternatively, following **GP4** with (*R*,*R*)-**T2**, the diastereomeric substrate (*Z*)-**41c** (55 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*R*,5*S*)-**42c** (62 mg, 83%; 96:4 dr, determined via ^{31}P NMR analysis) as a colorless viscous liquid. Characterization data for (2*R*,5*S*)-**42c**: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +10.8° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, C_6D_6) δ 7.42 (2H, d, *J* = 7.5 Hz, n), 7.17 (2H, t, *J* = 7.5 Hz, o), 7.02 (1H, t, *J* = 7.5 Hz, p), 3.97-3.83 (5H, m, b+b'+g), 3.68 (1H, dd, *J* = 7.5, 6.0 Hz, h(1H)), 3.30 (1H, t, *J* = 7.5 Hz, h(1H)), 2.62-2.26 (4H, m, c+e), 1.75-1.70 (1H, m, f), 1.33 (j or j'), 1.33-1.28 (1H, m, f(1H)), 1.27 (3H, s, j or j'), 1.16 (6H, s, l or l'), 1.13 (6H, s, l or l'), 1.08-1.06 (6H, m, a+a') ppm; ^{13}C NMR (175 MHz, C_6D_6) δ 145.37 (d, $^{3}J_{C\text{-}P}$ = 18

Hz, m), 128.87 (o), 127.79 (n), 126.19 (p), 108.86 (i), 84.23 (k), 77.34 (g), 70.13 (h), 61.47 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.10 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 32.80 (d, $^{3}J_{C\text{-}P}$ = 5.0 Hz, e), 31.45 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 28.79 (f), 27.55 (j or j'), 26.31 (j or j'), 25.46 (l or l'), 25.27 (l or l'), 16.91 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.85 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, C_6D_6) δ 33.02 (br s) ppm; ^{31}P NMR (283 MHz, C_6D_6) δ 32.30 (4%; minor diastereomer), 32.18 (96%; major diastereomer) ppm; IR (neat) 2979 (aromatic C-H), 2934 (aliphatic C-H), 1369 (aromatic C=C), 1320 (aromatic C=C), 1241 (P=O), 1143, 1052 (C-O), 1025 (C-O), 954 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{25}H_{42}BO_7P$ = 496.2761, found 496.2780 *m/z*.



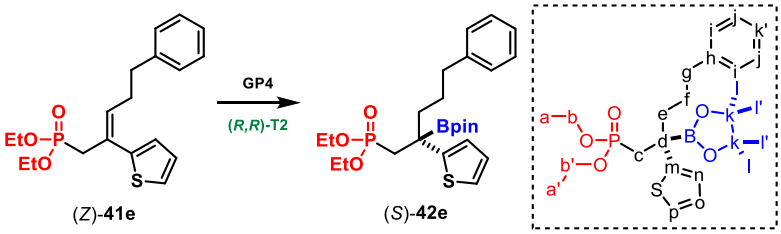
Synthesis of chiral tertiary benzylic boronic ester (2*S*,5*S*)-42c: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) using (*S*,*S*)-**T2**, the substrate (*E*)-**41c** (55 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*S*,5*S*)-**42c** (58 mg, 78%; 85:15 dr, determined via ^{31}P NMR analysis) as a colorless viscous liquid. Alternatively, following **GP4** with (*S*,*S*)-**T2**, the diastereomeric substrate (*Z*)-**41c** (55 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*S*,5*S*)-**42c** (63 mg, 84%; 97:3 dr, determined via ^{31}P NMR analysis) as a colorless viscous liquid. Characterization data for (2*S*,5*S*)-**42c**: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +6.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, C_6D_6) δ 7.45 (2H, d, *J* = 8.0 Hz, n), 7.17 (2H, dd, *J* = 8.0, 7.5 Hz, o), 7.02 (1H, t, *J* = 7.5 Hz, p), 3.96-3.82 (5H, m, b+b'+g), 3.75 (1H, dd, *J* =

7.5, 6.0 Hz, h(1H)), 3.40 (1H, t, *J* = 7.5 Hz, h(1H)), 2.62-2.25 (4H, m, c+e), 1.55-1.44 (2H, m, f), 1.35 (j or j'), 1.28 (3H, s, j or j'), 1.16 (6H, s, l or l'), 1.12 (6H, s, l or l'), 1.07-1.02 (6H, m, a+a') ppm; ^{13}C NMR (175 MHz, C_6D_6) δ 145.09 (d, $^{3}J_{C\text{-}P}$ = 17 Hz, m), 128.83 (o), 127.91 (n), 126.18 (p), 108.86 (i), 84.22 (k), 77.22 (g), 69.94 (h), 61.61 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.00 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 32.68 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, e), 31.70 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 29.03 (f), 27.66 (j or j'), 26.36 (j or j'), 25.39 (l or l'), 25.30 (l or l'), 16.90 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.80 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, C_6D_6) δ 32.71 (br s) ppm; ^{31}P NMR (283 MHz, C_6D_6) δ 32.30 (97%; major diastereomer), 32.18 (3%; major diastereomer) ppm; IR (neat) 2979 (aromatic C-H), 2933 (aliphatic C-H), 1369 (aromatic C=C), 1320 (aromatic C=C), 1240 (P=O), 1143, 1051 (C-O), 1024 (C-O), 954 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{25}H_{42}BO_7P$ = 496.2761, found 496.2781 *m/z*.



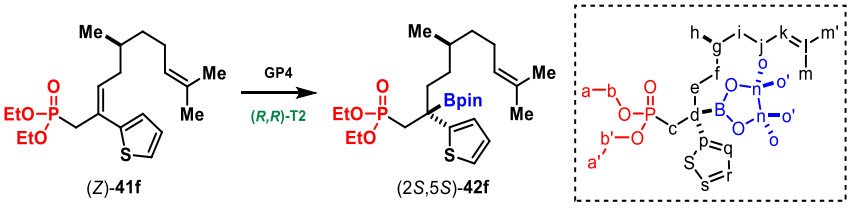
Synthesis of chiral tertiary benzylic boronic ester (*R*)-42d: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) using (*R*,*R*)-**T2**, the substrate (*E*)-**41d** (50 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (*R*)-**42d** (41 mg, 60%) as a colorless liquid. Alternatively, following **GP4** with (*R*,*R*)-**T2**, the diastereomeric substrate (*Z*)-**41d** (50 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (*R*)-**42d** (49 mg, 71%). Characterization data of (*R*)-**42d**: TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = +55° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (4H, m, aryl), 7.19-7.10 (6H, m, aryl), 7.08-3.71 (4H, m, b+b'), 3.48 (1H, dd,

J = 71, 14 Hz, e), 2.43-2.20 (2H, m, c), 1.29-1.16 (18H, m, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.00 (d, $^3J_{C\text{-}P}$ = 13.0 Hz, l), 139.06 (f), 130.95 (aryl), 128.20 (aryl), 127.64 (aryl), 127.59 (aryl), 126.02 (aryl), 125.84 (aryl), 84.12 (j), 61.23 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 60.95 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 40.52 (d, $^3J_{C\text{-}P}$ = 3.75 Hz, e), 30.12 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 25.05 (k or k'), 24.99 (k or k'), 16.57 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.42 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.54 ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.81; IR (neat) 2978 (aromatic C-H), 2930 (aliphatic C-H), 1497 (aromatic C=C), 1379 (aromatic C=C), 1371 (aromatic C=C), 1321 (aromatic C=C), 1241 (P=O), 1051 (C-O), 1027 (C-O), 956 (P-O), 701 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol **43d**.



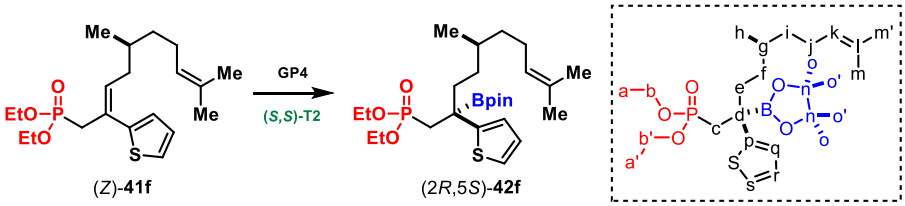
Synthesis of chiral tertiary benzylic boronic ester (*S*)-42e: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R,R*)-**T2**, the substrate (*Z*)-**41e** (56 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (*S*)-**42e** (63 mg, 85%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = -8.2° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.23 (2H, m, aryl), 7.18-7.13 (4H, m, aryl), 6.95 (1H, dd, *J* = 3.5, 1.0 Hz, o), 6.92 (1H, dd, *J* = 5.0, 3.5 Hz, n), 4.08-3.84 (4H, m, b+b'), 2.66-2.54 (2H, m, g), 2.42 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.37 (1H, dd, *J* = 18.0, 15.0 Hz, c), 2.18-2.07 (2H, m, e), 1.67-1.44 (2H, m, f), 1.30-1.23 (18H, m, a+a'+l+l') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.12 (d, $^3J_{C\text{-}P}$ = 17 Hz, m), 142.83 (h), 128.53

(aryl), 128.35 (aryl), 126.70 (n), 125.73 (aryl), 124.43 (o), 123.09 (aryl), 84.15 (k), 61.48 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.02 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 37.87 (d, $^{3}J_{C\text{-}P}$ = 8.0 Hz, e), 36.60 (g), 33.61 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 26.70 (f), 24.94 (l or l'), 24.90 (l or l'), 16.63 (d, $^{3}J_{C\text{-}P}$ = 7.0 Hz, a or a'), 16.56 (d, $^{3}J_{C\text{-}P}$ = 6.5 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.83 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.58 ppm; IR (neat) 2976 (aromatic C-H), 2933 (aliphatic C-H), 1371 (aromatic C=C), 1324 (aromatic C=C), 1241 (P=O), 1142, 1051 (C-O), 1024 (C-O/C=S), 958 (P-O), 696 cm^{-1}; The enantiomer ratio of this boronic ester is determined after oxidation to the chiral tertiary alcohol (*R*)-**43e**.



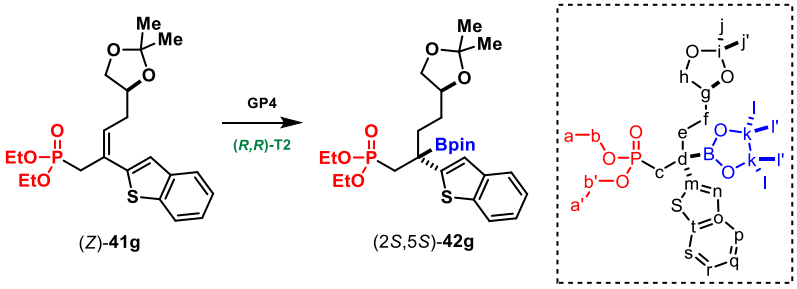
Synthesis of chiral tertiary benzylic boronic ester (2*S*,5*S*)-**42f:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2** (Note: 2 mol% catalyst loading was used), the substrate (*Z*)-**41f** (58 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*S*,5*S*)-**42f** (42 mg, 55%) as a colorless viscous liquid (Note: 2 mol% catalyst loading used. Even when higher catalyst loading is used, the reactions with this substrate did not proceed to complete consumption of substrate, perhaps due to the presence of three chelating sites leading to catalyst inactivation): TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = +9.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (1H, dd, *J* = 5.0, 1.0 Hz, s), 7.00 (1H, dd, *J* = 3.5, 1.0 Hz, r), 6.92 (1H, dd, *J* = 5.0, 3.5 Hz, q), 5.09-5.06 (1H, m, k), 4.07-3.78 (4H, m, b+b'), 2.45-2.32 (2H, m, c), 2.11-1.87 (4H, m, e+j), 1.68 (3H, s, m or m'), 1.58 (3H, s, m or m'), 1.44-1.20 (21H, a+a'+f+g+o+o'), 1.14-0.94 (2H, m, i), 0.87 (3H, d, *J* = 6.5 Hz, h) ppm; ^{13}C NMR (100 MHz,

$CDCl_3$) δ 150.34 (d, $^3J_{C\text{-}P}$ = 15 Hz, p), 131.07 (l), 126.63 (q), 125.24 (k), 124.70 (r), 123.02 (s), 84.12 (n), 61.38 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.03 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 37.33, 35.91 (d, $^3J_{C\text{-}P}$ = 8.5 Hz, e) , 34.11 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 33.15, 31.86, 25.90 (m or m'), 25.81, 25.01 (o *or* o'), 24.94 (o *or* o'), 19.71 (h), 17.83 (m or m'), 16.58 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.55 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.81 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.71 (92%; major diastereomer), 30.67 (8%; minor diastereomer) ppm; IR (neat) 2977 (aromatic C-H), 2933 (aliphatic C-H), 1373 (aromatic C=C), 1325 (aromatic C=C), 1239 (P=O), 1143, 1053 (C-O), 1025 (C-O/C=S), 958 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{26}H_{46}BO_5PS$ = 512.2897, found 512.2907 *m/z*.



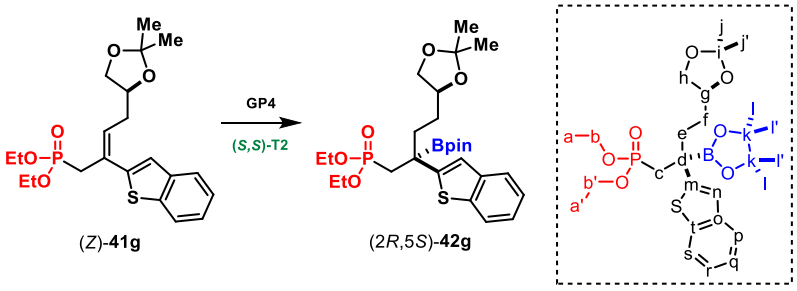
Synthesis of chiral tertiary benzylic boronic ester (2*R*,5*S*)-**42f:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) using (*S*,*S*)-**T2** (Note: 2 mol% catalyst loading was used), the substrate (*Z*)-**41f** (58 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*R*,5*S*)-**42f** (44 mg, 58%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:2) R_f = 0.5; $[\alpha]_D^{20}$ = +6.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (1H, dd, *J* = 5.0, 1.0 Hz, s), 7.00 (1H, dd, *J* = 3.5, 1.0 Hz, r), 6.92 (1H, dd, *J* = 5.0, 3.5 Hz, q), 5.07 (1H, t, *J* = 7.0 Hz, k), 4.09-3.75 (4H, m, b+b'), 2.45-2.31 (2H, m, c), 2.08-1.82 (4H, m, e+j), 1.68 (3H, s, m or m'), 1.58 (3H, s, m or m'), 1.42-1.04 (23H, a+a'+f+g+i+o+o'), 0.87 (3H, d, *J* = 6.5 Hz, h) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.34 (d, $^3J_{C\text{-}P}$ = 15 Hz, p), 131.07 (l), 126.63 (q), 125.25 (k), 124.77 (r), 84.12 (n), 61.39 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.02 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 37.13, 36.10 (d, $^3J_{C\text{-}P}$ = 9.0 Hz, e),

34.26 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 33.23, 31.79, 25.91, 25.74 (m or m'), 25.03 (o *or* o'), 24.95 (o *or* o'), 19.85 (h), 17.83 (m or m'), 16.58 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.55 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.41 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.71 (9%; minor diastereomer), 30.67 (91%; major diastereomer) ppm; IR (neat) 2978 (aromatic C-H), 2933 (aliphatic C-H), 1373 (aromatic C=C), 1325 (aromatic C=C), 1239 (P=O), 1143, 1053 (C-O), 1025 (C-O/C=S), 958 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{26}H_{46}BO_5PS$ = 512.2897, found 512.2900 *m/z*.



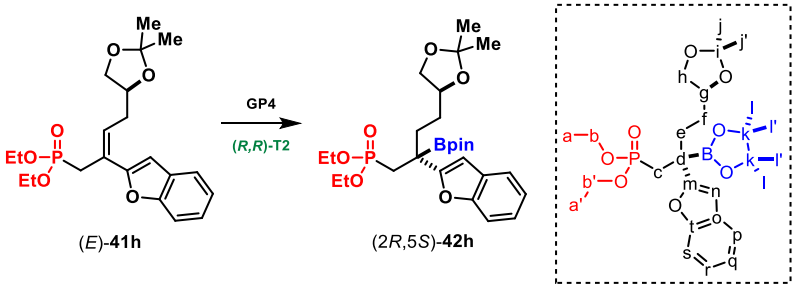
Synthesis of chiral tertiary benzylic boronic ester (2*S*,5*S*)-**42g:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate (*Z*)-**41g** (64 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*S*,5*S*)-**42g** (56 mg, 68%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +11.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, C_6D_6) δ 7.62-7.60 (2H, m, p+s), 7.26 (1H, s, n), 7.21-7.19 (1H, m, q or r), 7.10-7.07 (1H, m, q or r), 4.10-3.91 (5H, m, b+b'+g), 3.84-3.79 (1H, m, h(1H)), 3.51-3.43 (1H, m, h(1H)), 2.79-2.68 (2H, m, c(1H)+e(1H)), 2.58-2.54 (1H, m, c(1H)), 2.49-2.44 (1H, m, e(1H)), 1.96-1.91 (1H, m, f(1H)), 1.64-1.59 (1H, m, f(1H)), 1.43 (3H, s, j or j'), 1.37 (3H, s, j or j'), 1.30 (6H, s, l or l'), 1.25 (6H, s, l or l'), 1.15 (3H, t, *J* = 7.0 Hz, a or a'), 1.09 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (175 MHz, C_6D_6) δ 152.07 (d, $^{3}J_{C\text{-}P}$ = 20 Hz, m), 141.01 (*o* or t), 140.07 (*o* or t),

124.71 (q or r), 124.25 (q or r), 123.62 (p or s), 122.70 (p or s), 121.79 (n), 109.98 (i), 84.73 (k), 77.20 (g), 70.05 (h), 61.70 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.34 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 34.71 (d, $^{3}J_{C\text{-}P}$ = 6.5 Hz, e), 33.40 (d, $^{1}J_{C\text{-}P}$ = 141 Hz, c), 28.95 (f), 27.55 (j or j'), 26.25 (j or j'), 25.49 (l or l'), 25.38 (l or l'), 16.82 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.79 (d, $^{3}J_{C\text{-}P}$ = 5.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, C_6D_6) δ 34.00 (br s) ppm; ^{31}P NMR (283 MHz, C_6D_6) δ 30.55 (92%; major diastereomer), 30.51 (8%; minor diastereomer) ppm; IR (neat) 2980 (aromatic C-H), 2933 (aliphatic C-H), 1370 (aromatic C=C), 1329 (aromatic C=C), 1239 (P=O), 1141, 1052 (C-O), 1024 (C-O/C=S), 960 (P-O), 734 cm^{-1}; HRMS (EI) calculated for $C_{27}H_{42}BO_7PS$ = 552.2482, found 552.2499 *m/z*.



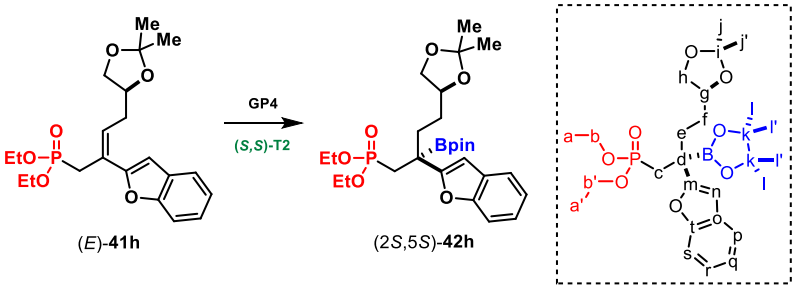
Synthesis of chiral tertiary benzylic boronic ester (2*R*,5*S*)-**42g:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*S*,*S*)-**T2**, the substrate (*Z*)-**41g** (64 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*R*,5*S*)-**42g** (57 mg, 69%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +5.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, C_6D_6) δ 7.63-7.60 (2H, m, p+s), 7.43 (1H, s, n), 7.20-7.18 (1H, m, q or r), 7.11-7.08 (1H, m, q or r), 4.08-3.94 (4H, m, b+b'), 3.89-3.80 (2H, m, g+h(1H)), 3.51-3.47 (1H, m, h(1H)), 2.74-2.67 (2H, m, c(1H)+e(1H)), 2.58-2.52 (1H, m, c(1H)), 2.39-2.35 (1H, m, e(1H)), 1.81-1.72 (2H, m, f), 1.46 (3H, s, j or j'), 1.38 (3H, s, j or j'), 1.32 (6H, s, l or l'), 1.26 (6H, s, l or l'), 1.11 (3H, t, *J* = 7.0 Hz, a or

a'), 1.02 (3H, t, J = 7.0 Hz, a or a') ppm; ^{13}C NMR (175 MHz, C_6D_6) δ 151.79 (d, $^{3}J_{C\text{-}P}$ = 18 Hz, m), 141.05 (*o* or t), 140.07 (*o* or t), 124.65 (q or r), 124.22 (q or r), 123.67 (p or s), 122.69 (p or s), 122.42 (n), 109.05 (i), 84.71 (k), 77.08 (g), 69.90 (h), 61.74 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.20 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 35.23 (d, $^{3}J_{C\text{-}P}$ = 9.0 Hz, e), 34.36 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 29.52 (f), 27.65 (j or j'), 26.32 (j or j'), 25.49 (l or l'), 25.46 (l or l'), 16.78 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.72 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, C_6D_6) δ 33.96 (br s) ppm; ^{31}P NMR (283 MHz, C_6D_6) δ 30.55 (8%; minor diastereomer), 30.51 (92%; major diastereomer) ppm; IR (neat) 2980 (aromatic C-H), 2933 (aliphatic C-H), 1372 (aromatic C=C), 1333 (aromatic C=C), 1239 (P=O), 1141, 1050 (C-O), 1023 (C-O/C=S), 958 (P-O), 735 cm^{-1}; HRMS (EI) calculated for $C_{27}H_{42}BO_7PS$ = 552.2482, found 552.2496 *m/z*.



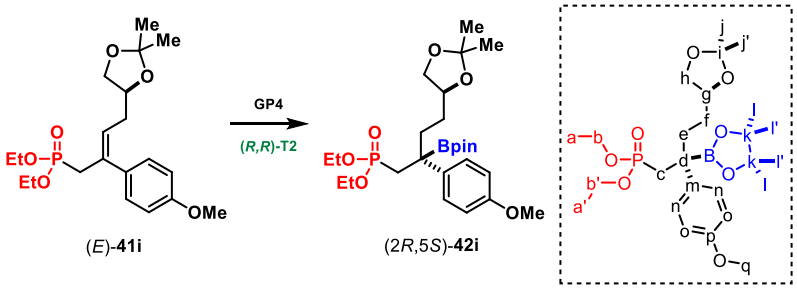
Synthesis of chiral tertiary benzylic boronic ester (2*R*,5*S*)-**42h:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate (*E*)-**41h** (61 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*R*,5*S*)-**42h** (61 mg, 76%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +5.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, C_6D_6) δ 7.40-7.36 (2H, m, p+s), 7.07-7.01 (2H, m, q+r), 6.85 (1H, s, n), 3.93-3.60 (6H, m, b+b'+g+h(1H)), 3.41-3.38 (1H, m, h(1H)), 2.63 (1H, dd, J = 15.0, 17.5 Hz, c(1H)), 2.51 (1H, dd, J = 15.0, 17.5 Hz, c(1H)),

2.48-2.43 (1H, m, e(1H)), 2.30-2.19 (1H, m, e(1H)), 1.75-1.68 (1H, m, f(1H)), 1.61-1.56 (1H, m, f(1H)), 1.35 (3H, s, j or j'), 1.26 (3H, s, j or j'), 1.23 (6H, s, l or l'), 1.20 (6H, s, l or l'), 0.99 (3H, t, J = 7.0 Hz, a or a'), 0.80 (3H, t, J = 7.0 Hz, a or a') ppm; ^{13}C NMR (175 MHz, C_6D_6) δ 161.81 (d, $^{3}J_{C\text{-}P}$ = 14 Hz, m), 155.58 (t), 129.87 (o), 123.95 (q or *r*), 123.14 (q or *r*), 121.19 (p or s), 111.28 (p or s), 109.00 (i), 104.90 (n), 84.70 (k), 76.81 (g), 69.83 (h), 61.42 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.32 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 32.68 (d, $^{3}J_{C\text{-}P}$ = 11 Hz, e), 32.40 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 30.28 (f), 27.58 (j or j'), 26.23 (j or j'), 25.53 (l or l'), 25.46 (l or l'), 16.75 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.52 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, C_6D_6) δ 34.01 (br s) ppm; ^{31}P NMR (283 MHz, C_6D_6) δ 30.00 (7%; minor diastereomer), 29.95 (93%; major diastereomer) ppm; IR (neat) 2980 (aromatic C-H), 2932 (aliphatic C-H), 1455 (aromatic C=C), 1370 (aromatic C=C), 1242 (P=O), 1141, 1051 (C-O), 1024 (C-O), 960 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{27}H_{42}BO_8P$ = 536.2710, found 536.2733 *m/z*.



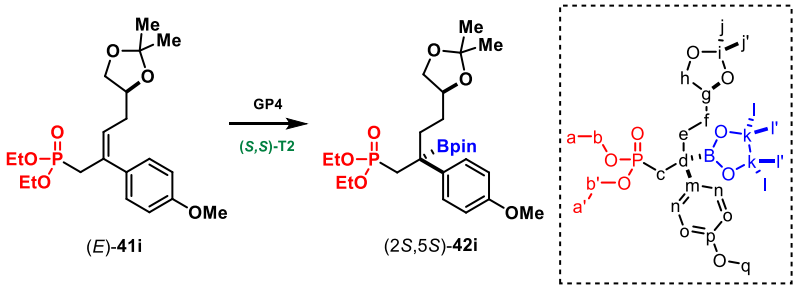
Synthesis of chiral tertiary benzylic boronic ester (2*S*,5*S*)-**42h:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*S*,*S*)-**T2**, the substrate (*E*)-**41h** (61 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*S*,5*R*)-**42h** (59 mg, 73%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +1.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, C_6D_6) δ 7.41-7.36 (2H, m, p+s), 7.07-

7.01 (3H, m, n+q+r), 3.92-3.56 (6H, m, b+b'+g+h(1H)), 3.31-3.29 (1H, m, h(1H)), 2.64 (1H, dd, *J* = 15.0, 17.5 Hz, c(1H)), 2.53-2.43 (2H, m, c(1H)+e(1H)), 2.23-2.19 (1H, m, e(1H)), 1.74-1.66 (1H, m, f(1H)), 1.51-1.66 (1H, m, f(1H)), 1.36 (3H, s, j or j'), 1.27 (9H, s, j or j' and l or l'), 1.23 (6H, s, l or l'), 1.00 (3H, t, *J* = 7.0 Hz, a or a'), 0.72 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (175 MHz, C_6D_6) δ 161.32 (d, $^{3}J_{C\text{-}P}$ = 12 Hz, m), 155.58 (t), 129.92 (o), 123.95 (q or *r*), 123.13 (q or *r*), 121.23 (p or s), 111.28 (p or s), 109.03 (i), 105.61 (n), 84.70 (k), 76.78 (g), 69.93 (h), 61.40 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.30 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 33.78 (d, $^{3}J_{C\text{-}P}$ = 14 Hz, e), 33.29 (d, $^{1}J_{C\text{-}P}$ = 141 Hz, c), 30.80 (f), 27.61 (j or j'), 26.28 (j or j'), 25.68 (l or l'), 25.46 (l or l'), 16.76 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.41 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, C_6D_6) δ 33.90 (br s) ppm; ^{31}P NMR (283 MHz, C_6D_6) δ 30.00 (80%; major diastereomer), 29.95 (20%; minor diastereomer) ppm; IR (neat) 2979 (aromatic C-H), 2933 (aliphatic C-H), 1454 (aromatic C=C), 1370 (aromatic C=C), 1242 (P=O), 1141, 1052 (C-O), 1024 (C-O), 961 (P-O) cm^{-1}; HRMS (EI) calculated for $C_{27}H_{42}BO_8P$ = 536.2710, found 536.2696 *m/z*.



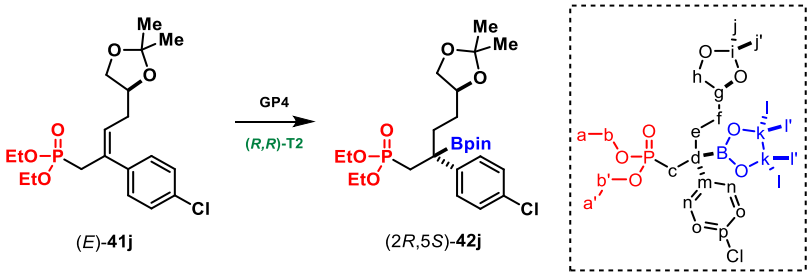
Synthesis of chiral tertiary benzylic boronic ester (2*R*,5*S*)-**42i:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) using (*R*,*R*)-**T2**, the substrate (*E*)-**41i** (60 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*R*,5*S*)-**42i** (59 mg, 75%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5;

$[\alpha]_D^{20}$ = +22° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, C_6D_6) δ 7.35 (2H, d, *J* = 8.5 Hz, n), 6.81 (2H, d, *J* = 8.5 Hz, o), 4.00-3.87 (5H, m, b+b'+g), 3.73 (1H, dd, *J* = 7.5, 6.5 Hz, h(1H)), 3.36 (1H, t, *J* = 7.5 Hz, h(1H)), 3.31 (3H, s, q), 2.58-2.29 (4H, m, c+e), 1.79-1.73 (1H, m, f(1H)), 1.38-1.32 (1H, m, f(1H)), 1.35 (3H, s, j or j'), 1.29 (3H, s, j or j'), 1.19 (6H, s, l or l'), 1.15 (6H, s, l or l'), 1.08 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (175 MHz, C_6D_6) δ 158.52 (p), 137.02 (d, $^3J_{C\text{-}P}$ = 18 Hz, m), 128.74 (n), 114.38 (o), 108.89 (i), 84.19 (k), 77.40 (g), 70.17 (h), 61.49 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.13 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 55.04 (q), 32.90 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, e), 31.75 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 28.81 (f), 27.58 (j or j'), 28.30 (j or j'), 25.49 (l or l'), 25.31 (l or l'), 16.92 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.86 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, C_6D_6) δ 34.66 (br s) ppm; ^{31}P NMR (283 MHz, C_6D_6) δ 32.40 (10%; minor diastereomer), 32.29 (90%; major diastereomer) ppm; IR (neat) 2980 (aromatic C-H), 2934 (aliphatic C-H), 1608, 1510, 1378 (aromatic C=C), 1245 (P=O), 1142, 1052 (C-O), 1026 (C-O), 955 (P-O), 835, 733 cm^{-1}; HRMS (EI) calculated for $C_{26}H_{44}BO_8P$ = 526.2867, found 526.2868 *m/z*.



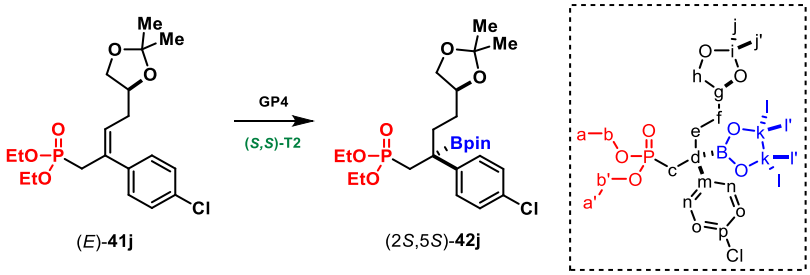
Synthesis of chiral tertiary benzylic boronic ester (2*S*,5*S*)-**42i:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*S*,*S*)-**T2**, the substrate (*E*)-**41i** (60 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*S*,5*S*)-**42i** (59 mg, 75%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5;

$[\alpha]_D^{20}$ = +13.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, C_6D_6) δ 7.38 (2H, d, *J* = 8.5 Hz, n), 6.82 (2H, d, *J* = 8.5 Hz, o), 4.00-3.85 (5H, m, b+b'+g), 3.78 (1H, t, *J* = 7.5 Hz, h(1H)), 3.43 (1H, t, *J* = 7.5 Hz, h(1H)), 3.31 (3H, s, q), 2.61-2.25 (4H, m, c+e), 1.59-1.51 (1H, m, f(1H)), 1.38 (3H, s, j or j'), 1.30 (3H, s, j or j'), 1.18 (6H, s, l or l'), 1.14 (6H, s, l or l'), 1.07 (3H, t, *J* = 7.0 Hz, a or a'), 1.05 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (175 MHz, C_6D_6) δ 158.51 (p), 136.78 (d, $^3J_{C\text{-}P}$ = 17.5 Hz, m), 128.88 (n), 114.35 (o), 108.94 (i), 84.17 (k), 77.31 (g), 70.00 (h), 61.61 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.00 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 55.04 (q), 32.82 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, e), 31.94 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 28.97 (f), 27.69 (j or j'), 26.37 (j or j'), 25.43 (l or l'), 25.35 (l or l'), 16.92 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, a or a'), 16.86 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, C_6D_6) δ 34.52 (br s) ppm; ^{31}P NMR (283 MHz, C_6D_6) δ 32.40 (90%; major diastereomer), 32.29 (10%; minor diastereomer) ppm; IR (neat) 2982 (aromatic C-H), 2937 (aliphatic C-H), 1608, 1510 , 1379 (aromatic C=C), 1246 (P=O), 1142, 1051 (C-O), 1027 (C-O), 958 (P-O), 835, 732 cm^{-1}; HRMS (EI) calculated for $C_{26}H_{44}BO_8P$ = 526.2867, found 526.2881 *m/z*.



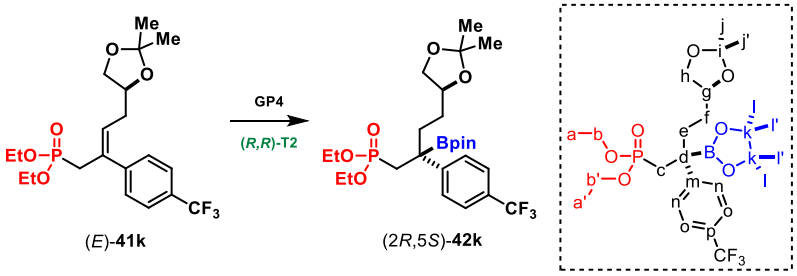
Synthesis of chiral tertiary benzylic boronic ester (2*R*,5*S*)-42j: Following the general procedure for catalytic asymmetric hydroboration (**GP4**) using (*R*,*R*)-**T2**, the substrate (*E*)-**41j** (60 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*R*,5*S*)-**42j** (50 mg, 63%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +3.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.5 Hz, n

or o), 7.27 (2H, d, *J* = 8.5 Hz, n or o), 4.03-3.88 (6H, m, b+b'+g+h(1H)), 3.42-3.40 (1H, m, h(1H)), 2.37-2.28 (2H, m, c), 2.22-2.15 (1H, m, e(1H)), 2.01-1.94 (1H, m, e(1H)), 1.58-1.53 (1H, m, f(1H)), 1.38-1.32 (7H, m, f(1H)+j+j'), 1.28-1.20 (18H, m, a+a'+l+l') ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 142.70 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, m), 131.62 (p), 128.77 (n or o), 128.46 (n or o), 108.74 (i), 84.19 (k), 76.56 (g), 69.71 (h), 61.48 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.12 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 31.55 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, e), 31.36 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 28.91 (f), 27.07 (j or j'), 25.86 (j or j'), 24.94 (l+l'), 16.55 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.54 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.02 (br s) ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 31.35 (17%; minor diastereomer), 31.16 (83%; major diastereomer) ppm; IR (neat) 2979 (aromatic C-H), 2935 (aliphatic C-H), 1492, 1510, 1369 (aromatic C=C), 1325 (aromatic C=C), 1240 (P=O), 1142, 1052 (C-O), 1026 (C-O), 958 (P-O), 836, 729 (C-Cl) cm^{-1}; HRMS (EI) calculated for $C_{25}H_{41}BClO_7P$ = 530.2372, found 530.2391 *m/z*.



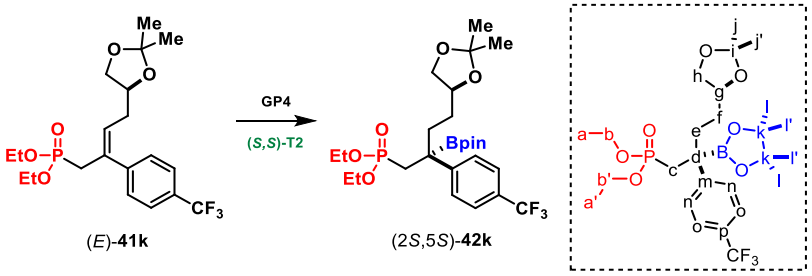
Synthesis of chiral tertiary benzylic boronic ester (2*S*,5*S*)-**42j:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*S*,*S*)-**T2**, the substrate (*E*)-**41j** (60 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*S*,5*S*)-**42j** (48 mg, 60%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +2.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 8.5 Hz, n or o), 7.27 (2H, d, *J* = 8.5 Hz, n or o), 4.08-3.89 (6H, m, b+b'+g+h(1H)), 3.50-3.48 (1H,

m, h(1H)), 2.44-2.28 (2H, m, c), 2.22-2.15 (1H, m, e(1H)), 2.02-1.95 (1H, m, e(1H)), 1.39-1.31 (8H, m, f+j+j'), 1.28-1.20 (18H, m, a+a'+l+l') ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 142.55 (d, $^{3}J_{C\text{-}P}$ = 15.0 Hz, m), 131.63 (p), 128.77 (n or o), 128.46 (n or o), 108.73 (i), 84.18 (k), 76.59 (g), 69.61 (h), 61.61 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.10 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 31.47 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, e), 31.17 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 28.78 (f), 27.11 (j or j'), 25.88 (j or j'), 24.94 (l or l'), 24.92 (l or l'), 16.59 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.56 (d, $^{3}J_{C\text{-}P}$ = 5.0 Hz, a or a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.56 (br s) ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 31.35 (83%; major diastereomer), 31.16 (17%; minor diastereomer) ppm; IR (neat) 2979 (aromatic C-H), 2934 (aliphatic C-H), 1491, 1511, 1369 (aromatic C=C), 1324 (aromatic C=C), 1242 (P=O), 1141, 1052 (C-O), 1028 (C-O), 959 (P-O), 836, 732 (C-Cl) cm^{-1}; HRMS (EI) calculated for $C_{25}H_{41}BClO_7P$ = 530.2372, found 530.2393 *m/z*.



Synthesis of chiral tertiary benzylic boronic ester (2*R*,5*S*)-**42k:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) with (*R*,*R*)-**T2**, the substrate (*E*)-**41k** (65 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*R*,5*S*)-**42k** (57 mg, 56%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +4.9° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.5 Hz, o), 7.50 (2H, d, *J* = 8.5 Hz, n), 4.06-3.83 (6H, m, b+b'+g+h(1H)), 3.46-3.41 (1H, m, h(1H)), 2.43-2.30 (2H, m, c), 2.26-2.18 (1H, m, e(1H)), 2.09-1.98 (1H, m, e(1H)), 1.59-1.49 (1H, m, f(1H)), 1.40-1.30 (7H, m, h(1H)+j+j'), 1.29-1.19 (18H, m, a+a'+l+l') ppm; ^{13}C NMR

(100 MHz, $CDCl_3$) δ 148.52 (d, $^3J_{C\text{-}P}$ = 12.0 Hz, m), 129.13 (q, $^2J_{C\text{-}F}$ = 32.0 Hz, p), 127.82 (n), 125.23 (q, $^3J_{C\text{-}F}$ = 3.75 Hz, o), 124.54 (q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 108.79 (i), 84.33 (k), 76.49 (g), 69.68 (h), 61.46 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.15 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 31.68 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 31.68 (d, $^3J_{C\text{-}P}$ = 7.0 Hz, e), 29.11 (f), 27.06 (j or j'), 25.85 (j or j'), 24.96 (l or l'), 24.95 (l or l'), 16.48 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.71 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.00 (13%; minor diastereomer), 30.75 (87%; major diastereomer) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.37 (85%; major diastereomer), -62.39 (15%; minor diastereomer) ppm; IR (neat) 2982 (aromatic C-H), 2932 (aliphatic C-H), 1617, 1370 (aromatic C=C), 1326 (aromatic C=C/C-F), 1240 (P=O), 1120, 1051 (C-O), 1025 (C-O), 959 (P-O), 844, 735, 678 cm^{-1}; HRMS (EI) calculated for $C_{26}H_{41}BF_3O_7P$ = 564.2635, found 564.2654 *m/z*.



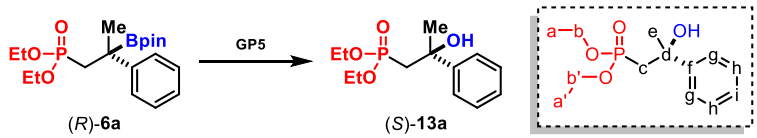
Synthesis of chiral tertiary benzylic boronic ester (2*S*,5*S*)-**42k:** Following the general procedure for catalytic asymmetric hydroboration (**GP4**) using (*S*,*S*)-**T2**, the substrate (*E*)-**41k** (65 mg, 0.15 mmol) yields the tertiary benzylic boronic ester product (2*S*,5*S*)-**42k** (58 mg, 57%) as a colorless viscous liquid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +2.9° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, d, *J* = 8.5 Hz, o), 7.50 (2H, d, *J* = 8.5 Hz, n), 4.06-3.85 (6H, m, b+b'+g+h(1H)), 3.52-3.45 (1H, m, h(1H)), 2.43-2.35 (2H, m, c), 2.31-2.19 (1H, m, e(1H)), 2.09-1.98 (1H, m, e(1H)), 1.43-1.32 (8H, m, h+j+j'), 1.26-1.15 (18H, m, a+a'+l+l') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.38 (d,

$^{3}J_{C\text{-}P}$ = 15.0 Hz, m), 129.12 (q, $^{2}J_{C\text{-}F}$ = 32.0 Hz, p), 127.77 (n), 125.24 (q, $^{3}J_{C\text{-}F}$ = 3.75 Hz, o), 124.88 (q, $^{1}J_{C\text{-}F}$ = 272 Hz, CF_3), 108.78 (i), 84.31 (k), 76.49 (g), 69.55 (h), 61.60 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.14 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 31.61 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 31.38 (d, $^{3}J_{C\text{-}P}$ = 7.0 Hz, e), 28.92 (f), 27.08 (j or j'), 25.84 (j or j'), 24.95 (l or l'), 24.91 (l or l'), 16.41 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.73 (br s) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.00 (85%; major diastereomer), 30.75 (15%; minor diastereomer) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.37 (17%; minor diastereomer), -62.39 (83%; major diastereomer) ppm; IR (neat) 2983 (aromatic C-H), 2932 (aliphatic C-H), 1618, 1369 (aromatic C=C), 1325 (aromatic C=C/C-F), 1241 (P=O), 1122, 1053 (C-O), 1025 (C-O), 958 (P-O), 845, 736, 681 cm^{-1}; HRMS (EI) calculated for $C_{26}H_{41}BF_3O_7P$ = 564.2635, found 564.2648 *m/z*.

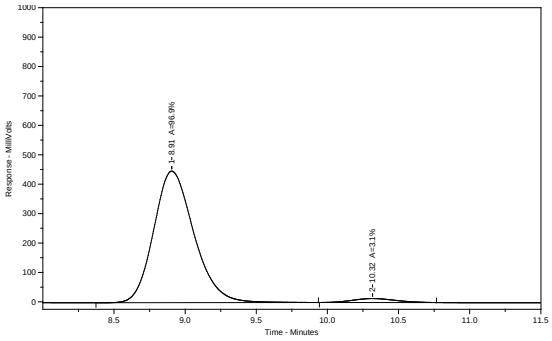
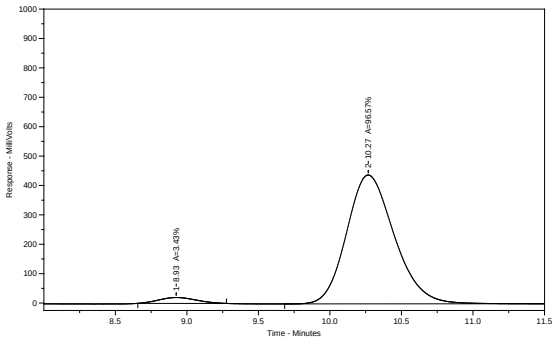
5.6. Oxidation Of Phosphonate-Functionalized Chiral Boronic Esters To Form Chiral Hydroxy Phosphonates

Representative procedure for oxidation of chiral tertiary benzylic boronic esters to the corresponding chiral tertiary benzylic alcohols (GP5): Oxidation of isolated and purified phosphonate-functionalized boronic esters is carried out as follows. (Note: Minor modifications in this procedure is carried out for different classes of chiral boronic esters). A mixture of the chiral boronic ester and $NaBO_3.4H_2O$ (5 equiv.) in THF/H_2O or THF/MeOH/H_2O is stirred vigorously for 9-12 hours. Afterwards, brine is added, and the reaction mixture extracted with ethyl acetate. The combined extracts are concentrated and purified via silica gel chromatography using varying combinations of ethyl-acetate, hexanes and methanol to afford the desired hydroxyphosphonates. Alternatively, for cases where the boronic ester is not easily isolable from the regioisomers or the reduced products,

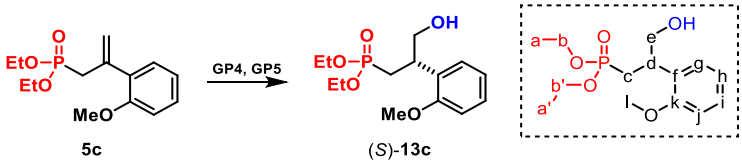
the CAHB mixture is partially purified using silica gel chromatography and the mixture of regioisomeric boronic esters and the reduced products are oxidized. Typically the regioisomeric alcohols were separable after oxidation.



Synthesis of chiral tertiary β-hydroxyphosphonate (*S*)-13a: Following **GP5**, the chiral boronic ester (*R*)-**6a** (57 mg, 0.15 mmol, 1.0 eq) affords the chiral tertiary β-hydroxyphosphonate (*S*)-**13a** (37 mg, 90%): TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; $[\alpha]_D^{20}$ = +2.5 º (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* = 8.0 Hz, g), 7.36 (2H, dd, *J* = 8.0, 7.5 Hz, h), 7.25 (1H, t, *J* = 7.5 Hz, i), 5.00 (1H, br s, OH), 4.14-4.00 (2H, m, b or b'), 3.78-3.67 (1H, m, b or b'), 3.45-3.35 (1H, m, b or b'), 2.53-2.32 (2H, m, c), 1.64 (3H, d, *J* = 2.5 Hz, e), 1.33 (3H, t, *J* = 7.0 Hz, a or a'), 1.02 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.40 (d, $^3J_{C\text{-}P}$ = 7.0 Hz, f), 128.31 (h), 126.94 (i), 124.98 (g), 72.18 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 61.95 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 61.63 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 39.93 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 32.68 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, e), 16.53 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a or a'), 16.28 (d, $^3J_{C\text{-}P}$ = 6.3 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.90 ppm; IR (neat) 3400 (O-H), 2979 (aromatic C-H), 2932 (aliphatic C-H), 1491 (aromatic C=C), 1446 (aromatic C=C), 1215 (P=O), 1048 (C-O), 1021 (C-O), 960 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{21}O_4P+Na^+$ = 295.1075, found 295.1081 *m/z*. Enantiomer ratio = 97:3, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AD; Mobile Phase = 95:5 Hexanes:Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

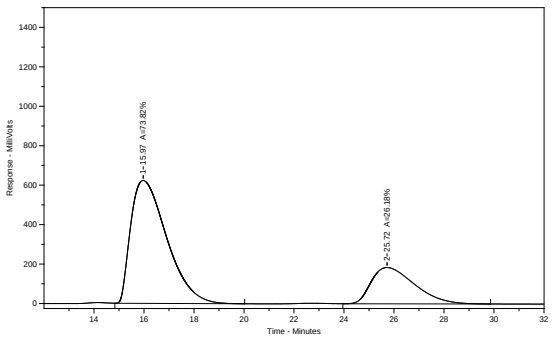
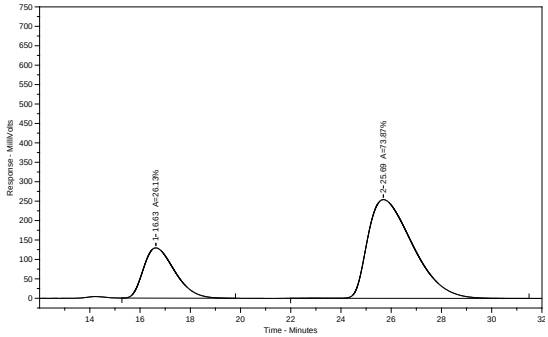
(a) R:S = 3:97, CAHB of **5a** with (*R*,*R*)-**T2**, then oxidation:	(b) R:S = 97:3, CAHB of **5a** with (*S*,*S*)-**T2**, then oxidation:
	

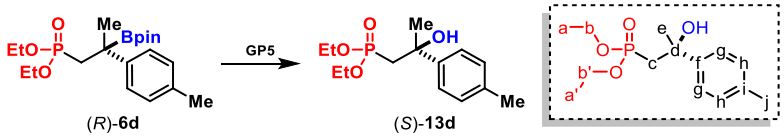
For characterization data for alcohol (*S*)-**13b** (Obtained from substrate **5b**), see section 5.11.2.



Synthesis of chiral primary alcohol (*S*)-13c: Following the general procedure for CAHB (**GP4**), the substrate **5c** (57 mg, 0.2 mmol) yields a mixture of boronic esters and reduced products that were not separable via silica gel chromatography. The crude CAHB mixture was chromatographed (ethyl acetate/hexanes 3:1) over silica gel to get rid of the non-polar colored complex and the polar metal residues. The crude mixture obtained after this partial purification was subjected to oxidation following **GP5** to obtain the chiral primary alcohol (*S*)-**13c** (48 mg, 80%) as a colorless oil: TLC analysis (ethyl acetate/methanol 19:1) R_f = 0.5; $[\alpha]_D^{20}$ = +4.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.19 (2H, m, aryl), 7.94 (1H, t, *J* = 7.5 Hz, aryl), 6.88 (1H, d, *J* = 8.0 Hz, j), 4.10-4.01 (4H, m, b+b'), 3.87-3.84 (5H, m, e+l), 3.67-3.58 (1H, m, d), 3.27 (1H, br s, OH), 2.32 (1H, ddd, *J* = 18.0, 15.0, 8.5

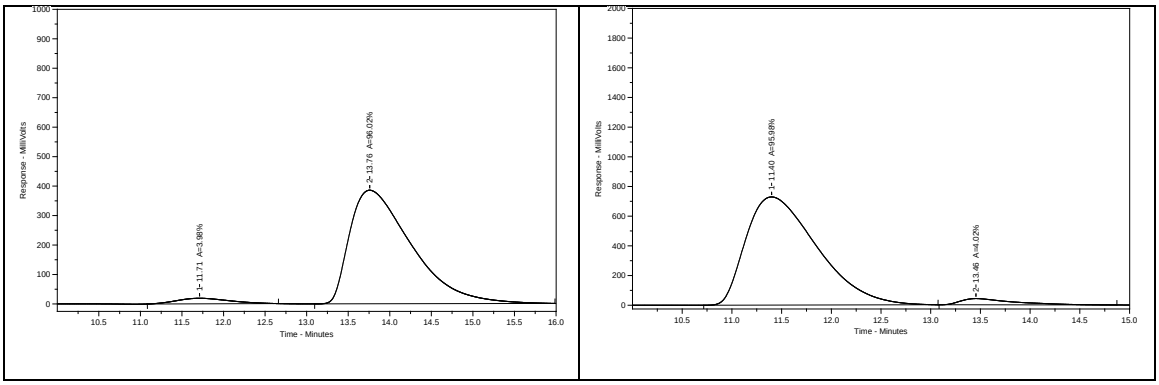
Hz, c(1H)), 2.19 (1H, ddd, *J* = 19.0, 18.0, 5.5 Hz, c(1H)), 1.30 (3H, t, *J* = 7.0 Hz, a or a'), 1.28 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.07 (k), 130.48 (d, $^{3}J_{C\text{-}P}$ = 12.5 Hz, f), 128.61 (aryl), 128.08 (aryl), 120.82 (aryl), 110.85 (j), 66.40 (d, $^{3}J_{C\text{-}P}$ = 8.0 Hz, e), 61.97 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.75 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 55.45 (l), 37.47 (d, $^{2}J_{C\text{-}P}$ = 2.0 Hz, d), 28.24 (d, $^{1}J_{C\text{-}P}$ = 139 Hz, c), 16.48 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.46 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.39 ppm; IR (neat) 3369 (O-H), 2980 (sp^2 C-H), 2907 (sp^3 C-H), 1493 (aromatic C=C), 1391 (aromatic C=C), 1239 (P=O), 1020 (C-O), 958 (P-O), 752 cm^{-1}. HRMS (ESI) calculated for $C_{14}H_{23}O_5P$+Na^+ = 325.1181, found 325.1184 *m/z*. Enantiomer ratio = 74:26, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile phase = 90:10 Hexanes: Isopropanol; Flow rate = 1.5 mL/min. HPLC UV detector λ = 220 nm, rt. HPLC traces:

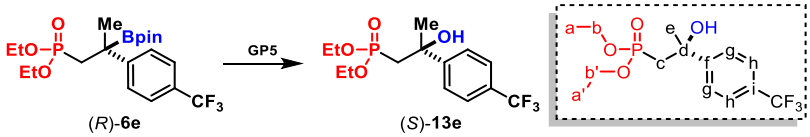
(a) R:S = 26:74, CAHB of **5c** with (*R*,*R*)-**T2**, then oxidation to yield **13c**:	(b) R:S = 74:26, CAHB of **5c** with (*S*,*S*)-**T2**, then oxidation to yield **13c**:
	



Synthesis of chiral tertiary benzyl alcohol (*S*)-13d: Following **GP5**, the chiral boronic ester (*R*)-**6d** (40 mg, 0.10 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13d** (28 mg, 91%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = -8.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.0 Hz, g), 7.16 (2H, d, *J* = 8.0 Hz, h), 4.94 (1H, br s, OH), 4.14-4.00 (2H, m, b or b'), 3.79-3.69 (1H, m, b or b'), 3.49-3.40 (1H, m, b or b'), 2.49-2.29 (5H, m, c+j), 1.62 (3H, d, $^4J_{P-H}$ = 2.0 Hz, e), 1.32 (3H, t, *J* = 7.0 Hz, a or a'), 1.03 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.49 (d, $^3J_{C-P}$ = 7.5 Hz, f), 136.43 (i), 128.91 (h), 124.82 (g), 72.04 (d, $^2J_{C-P}$ = 5.0 Hz, d), 61.93 (d, $^2J_{C-P}$ = 6.5 Hz, b or b'), 61.56 (d, $^2J_{C-P}$ = 6.5 Hz, b or b'), 39.95 (d, $^1J_{C-P}$ = 135 Hz, c), 32.58 (d, $^3J_{C-P}$ = 14.0 Hz, e), 21.07 (j), 16.49 (d, $^3J_{C-P}$ = 6.0 Hz, a or a'), 16.22 (d, $^3J_{C-P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.98 ppm; IR (neat) 3397 (O-H), 2979 (aromatic C-H), 2923 (aliphatic C-H), 1513 (aromatic C=C), 1392 (aromatic C=C), 1214 (P=O), 1019 (C-O), 960 (P-O), 819 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_4P+Na^+$ = 309.1232, found 309.1238 *m/z*. Enantiomer ratio = 96:4, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AS-H; Mobile phase = 95:5 Hexanes:Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

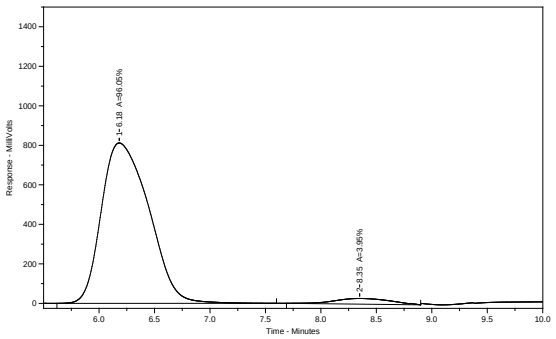
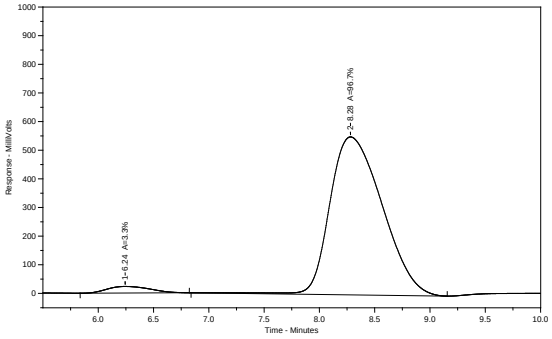
(a) R:S = 4:96, CAHB of **5d** with (*R*,*R*)-**T2**, then oxidation to yield **13d**:	(b) R:S = 96:4, CAHB of **5d** with (*S*,*S*)-**T2**, then oxidation to yield **13d**:

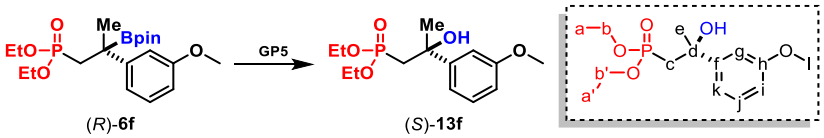




Synthesis of chiral tertiary benzyl alcohol (*S*)-13e: Following **GP5**, the chiral boronic ester (*R*)-**6e** (45 mg, 0.10 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13e** (28 mg, 83%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +10.2° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (4H, br s, g+h), 5.17 (1H, br s, OH), 4.16-4.02 (2H, m, b or b'), 3.79-3.69 (1H, m, b or b'), 3.55-3.45 (1H, m, b or b'), 2.47 (1H, dd, *J* = 17.0, 15.0 Hz, c (1H)), 2.36 (1H, dd, *J* = 17.0, 15.0 Hz, c(1H)), 1.64 (3H, s, e), 1.34 (3H, t, *J* = 7.0 Hz, a or a'), 0.99 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.45 (d, $^3J_{C\text{-}P}$ = 7.5 Hz, f), 129.31 (q, $^2J_{C\text{-}F}$ = 32.0 Hz, i), 125.55 (g), 125.40 (d, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 125.25 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, h), 72.12 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 61.99 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.96 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 39.58 (d, $^1J_{C\text{-}P}$ = 136.0 Hz, c), 32.52 (d, $^3J_{C\text{-}P}$ = 14.5 Hz, e), 16.53 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.09 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.30 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.48 ppm; IR (neat) 3385 (O-H), 2982 (sp^2 C-H), 2933 (sp^3 C-H), 1618, 1444 (aromatic C=C), 1409 (aromatic C=C), 1325 (C-F), 1218 (P=O), 1049 (C-O), 1015

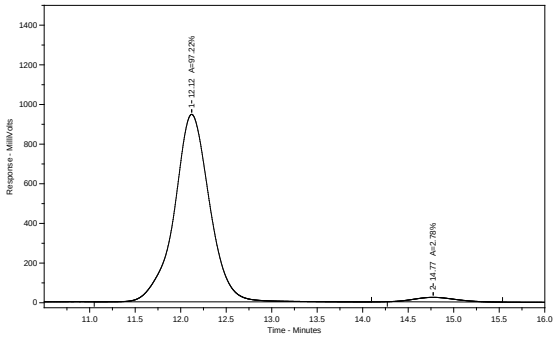
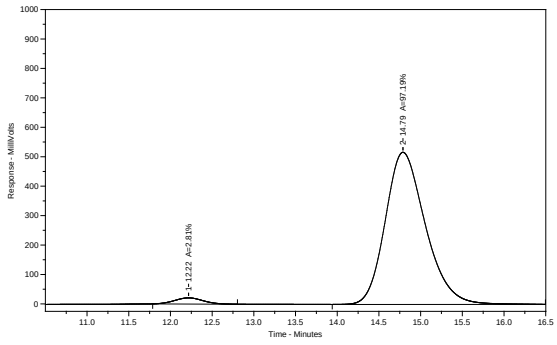
(C-O), 961 (P-O), 840 cm^{-1}. HRMS (ESI) calculated for $C_{14}H_{20}F_3O_4P+Na^+$ = 363.0949, found 363.0955 *m/z*. Enantiomer ratio = 96:4, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AD; Mobile phase = 95:5 Hexanes: Isopropanol; Flow rate = 1.25 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

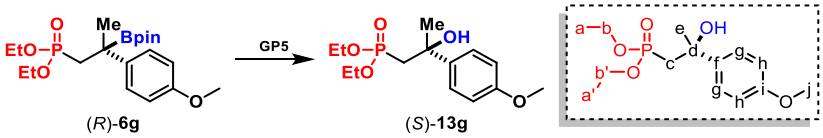
(a) R:S = 4:96, CAHB of **5e** with (*R*,*R*)-**T2**, then oxidation to yield **13e**:	(b) R:S = 96:4, CAHB of **5e** with (*S*,*S*)-**T2**, then oxidation to yield **13e**:
	



Synthesis of chiral tertiary benzyl alcohol (*S*)-13f: Following **GP5**, the chiral boronic ester (*R*)-**6f** (41 mg, 0.10 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13f** (26 mg, 85%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +3.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, t, *J* = 8.0 Hz, j), 7.09 (1H, t, *J* = 2.0 Hz, g), 7.02 (1H, d, *J* = 8.0 Hz, k), 6.78 (1H, dd, *J* = 8.0, 2.0 Hz, i), 5.00 (1H, br s, OH), 4.11-4.05 (2H, m, b or b'), 3.84 (3H, s, l), 3.79-3.70 (1H, m, b or b'), 3.52-3.42 (1H, m, b or b'), 2.50-2.29 (2H, m, c), 1.61 (3H, d, $^4J_{P-H}$ = 2.0 Hz, e), 1.32 (3H, t, *J* = 7.0 Hz, a or a'), 1.04 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ

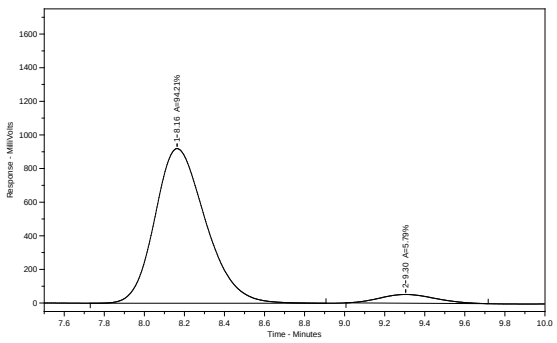
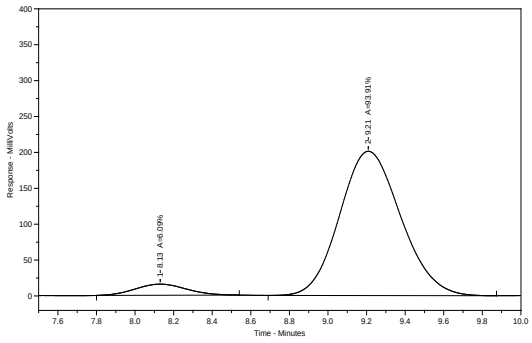
159.71 (h), 149.23 (d, $^{3}J_{C\text{-}P}$ = 7.5 Hz, f), 129.26 (j), 117.36 (k), 112.36 (g), 110.73 (i), 72.09 (d, $^{2}J_{C\text{-}P}$ = 5.0 Hz, d), 61.97 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.59 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 55.39 (l), 39.76 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 32.54 (d, $^{3}J_{C\text{-}P}$ = 14.0 Hz, e), 16.48 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.24 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.84 ppm; IR (neat) 3403 (O-H), 2979 (aromatic C-H), 2933 (aliphatic C-H), 1600, 1583, 1455 (aromatic C=C), 1390 (aromatic C=C), 1215 (P=O), 1020 (C-O), 961 (P-O), 781 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_5P$+Na^+ = 325.1181, found 325.1186 *m/z*. Enantiomer ratio = 97:3, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AD; Mobile phase = 95:5 Hexanes: Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

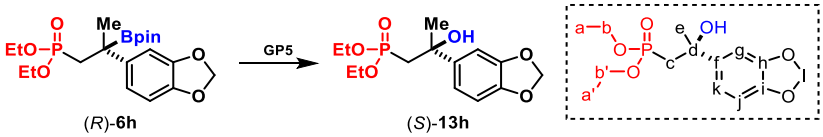
(a) R:S = 3:97, CAHB of **5f** with (*R*,*R*)-**T2**, then oxidation to yield **13f**:	(b) R:S = 97:3, CAHB of **5f** with (*S*,*S*)-**T2**, then oxidation to yield **13f**:
	



Synthesis of chiral tertiary benzyl alcohol (*S*)-13g: Following **GP5**, the chiral boronic ester (*R*)-**6g** (41 mg, 0.10 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13g**

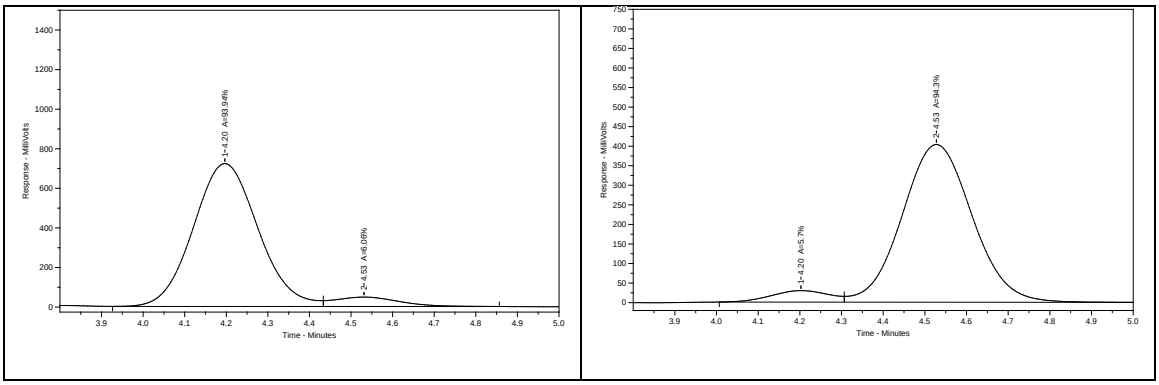
(24 mg, 78%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +2.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.75 Hz, g), 6.89 (2H, d, *J* = 8.75 Hz, h), 4.95 (1H, br s, OH), 4.14-3.99 (2H, m, b or b'), 3.81 (3H, s, j), 3.81-3.71 (1H, m, b or b'), 3.53-3.43 (1H, m, b or b'), 2.49-2.29 (2H, m, c), 1.61 (3H, d, $^4J_{P\text{-}H}$ = 2.0 Hz, e), 1.32 (3H, t, *J* = 7.0 Hz, a or a'), 1.06 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.59 (i), 139.69 (d, $^3J_{C\text{-}P}$ = 7.5 Hz, f), 126.12 (g), 113.59 (h), 71.92 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 61.96 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.60 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 55.49 (j), 39.98 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 32.71 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, e), 16.52 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.32 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.00 ppm; IR (neat) 3400 (O-H), 2980 (aromatic C-H), 2931 (aliphatic C-H), 1610, 1510, 1443 (aromatic C=C), 1391 (aromatic C=C), 1245 (P=O), 1021 (C-O), 961 (P-O), 832 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_5P+Na^+$ = 325.1181, found 325.1184 *m/z*. Enantiomer ratio = 94:6, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AD; Mobile phase = 90:10 Hexanes: Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

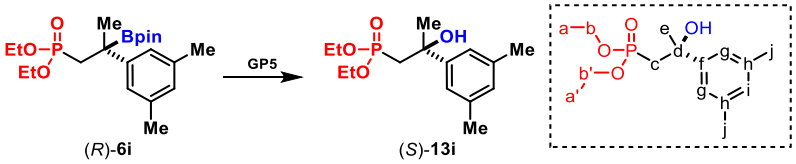
(a) R:S = 6:94, CAHB of **5g** with (*R*,*R*)-**T2**, then oxidation to yield **13g**:	(b) R:S = 94:6, CAHB of **5g** with (*S*,*S*)-**T2**, then oxidation to yield **13g**:
	



Synthesis of chiral tertiary benzyl alcohol (*S*)-13h: Following **GP5**, the chiral boronic ester (*R*)-**6h** (43 mg, 0.10 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13h** (24 mg, 75%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; $[\alpha]_D^{20}$ = +6.4° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, d, *J* = 2.0 Hz, g), 6.95 (1H, dd, *J* = 8.0, 2.0 Hz, k), 6.77 (1H, d, *J* = 8.0 Hz, j), 5.93 (2H, s, l), 4.95 (1H, br s, OH), 4.14-4.00 (2H, m, b or b'), 3.86-3.76 (1H, m, b or b'), 3.65-3.55 (1H, m, b or b'), 2.45-2.25 (2H, m, c), 1.59 (3H, d, $^4J_{P\text{-}H}$ = 2.0 Hz, e), 1.32 (3H, t, *J* = 7.0 Hz, a or a'), 1.10 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.147.64 (h or i), 146.38 (h or i), 141.78 (d, $^3J_{C\text{-}P}$ = 8.0 Hz, f), 118.02 (k), 107.89 (j), 106.09 (g), 101.10 (l), 72.05 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 61.98 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.66 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 39.89 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 32.65 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, e), 16.49 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a or a'), 16.29 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.79 ppm; IR (neat) 3397 (O-H), 2980 (aromatic C-H), 2908 (aliphatic C-H), 1488 (aromatic C=C), 1434 (aromatic C=C), 1231 (P=O), 1021 (C-O), 938 (P-O), 813, 730 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{21}O_6P+Na^+$ = 339.0973, found 339.0979 *m/z*. Enantiomer ratio = 94:6, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AD; Mobile phase = 60:40 Hexanes: Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

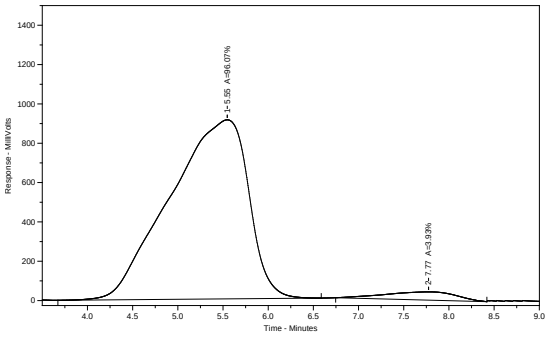
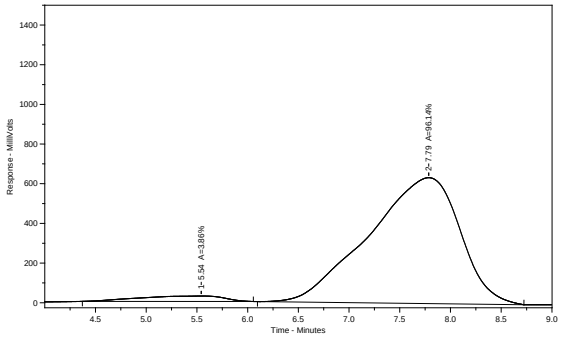
(a) R:S = 6:94, CAHB of **5h** with (*R*,*R*)-**T2**, then oxidation to yield **13h**:	(b) R:S = 94:6, CAHB of **5h** with (*S*,*S*)-**T2**, then oxidation to yield **13h**:

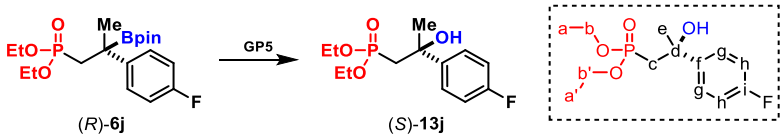




Synthesis of chiral tertiary benzyl alcohol (*S*)-13i: Following **GP5**, the chiral boronic ester (*R*)-**6i** (41 mg, 0.1 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13i** (25 mg, 83%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +7° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (2H, s, g), 6.88 (1H, s, i), 4.91 (1H, br s, OH), 4.14-4.00 (2H, m, b or b'), 3.80-3.70 (1H, m, b or b'), 3.51-3.41 (1H, m, b or b'), 2.49-2.29 (8H, m, c+j), 1.61 (3H, d, $^4J_{P\text{-}H}$ = 2.0 Hz, e), 1.33 (3H, t, *J* = 7.0 Hz, a or a'), 1.05 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.37 (d, $^3J_{C\text{-}P}$ = 8.0 Hz, f), 137.70 (h), 128.45 (i), 122.67 (g), 72.06 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 61.93 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.51 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 39.89 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 32.52 (d, $^3J_{C\text{-}P}$ = 13.5 Hz, e), 21.61 (j), 16.48 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a or a'), 16.22 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.05 ppm; IR (neat) 3407 (O-H), 2980 (sp^2 C-H), 2915 (sp^3 C-H), 1443 (aromatic C=C), 1392 (aromatic C=C), 1217 (P=O), 1051 (C-O), 1021 (C-O), 960 (P-O), 849 cm^{-1}. HRMS (ESI) calculated for $C_{15}H_{25}O_4P+Na^+$ = 323.1388 found 323.1392 *m/z*. Enantiomer ratio = 96:4, determined by chiral HPLC

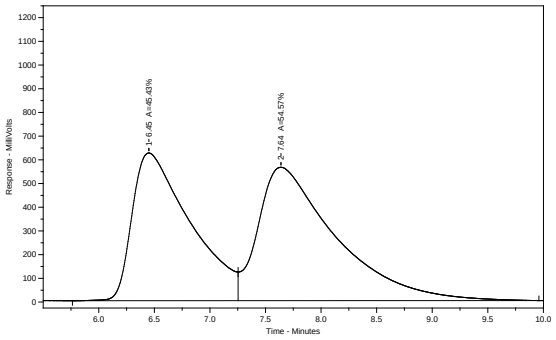
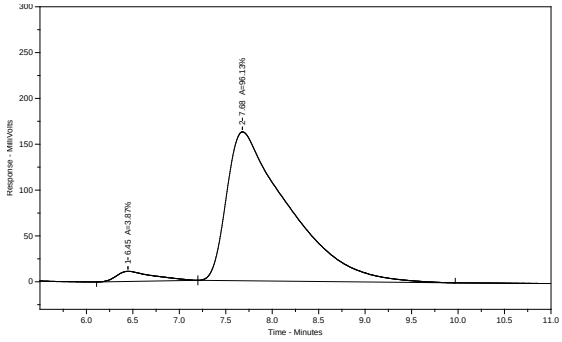
analysis: Stationary phase = CHIRALPAK IC; Mobile phase = 90:10 Hexanes: Isopropanol; Flow rate = 1.5 mL/min. HPLC UV detector λ = 220 nm, rt. HPLC traces:

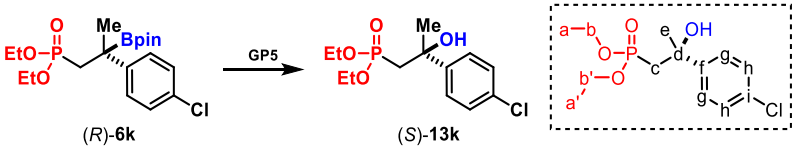
(a) R:S = 4:96, CAHB of **5i** with (*R*,*R*)-**T2**, then oxidation to yield **13i**:	(b) R:S = 96:4, CAHB of **5i** with (*S*,*S*)-**T2**, then oxidation to yield **13i**:
	



Synthesis of chiral tertiary benzyl alcohol (*S*)-13j: Following **GP5**, the chiral boronic ester (*R*)-**6j** (40 mg, 0.10 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13j** (23 mg, 80%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +4.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (2H, m, g), 7.05-6.99 (2H, m, h), 5.05 (1H, br s, OH), 4.14-4.00 (2H, m, b or b'), 3.80-3.81 (1H, m b or b'), 3.56-3.46 (1H, m, b or b'), 2.44 (1H, dd, *J* = 18.0, 15.0 Hz, c(1H)), 2.32 (1H, dd, *J* = 18.0, 15.0 Hz, c(1H)), 1.61 (3H, d, $^4J_{P\text{-}H}$ = 2.5 Hz, e), 1.32 (3H, t, *J* = 7.0 Hz, a or a'), 1.05 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.90 (d, $^1J_{C\text{-}F}$ = 245 Hz, i), 143.24 (dd, $^3J_{C\text{-}P}$ = 7.5 Hz, $^4J_{C\text{-}F}$ = 3.0 Hz, f), 126.74 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, g), 114.93 (d, $^2J_{C\text{-}F}$ = 21 Hz, h), 71.91 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 61.94 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.77 (d, $^3J_{C\text{-}P}$ =

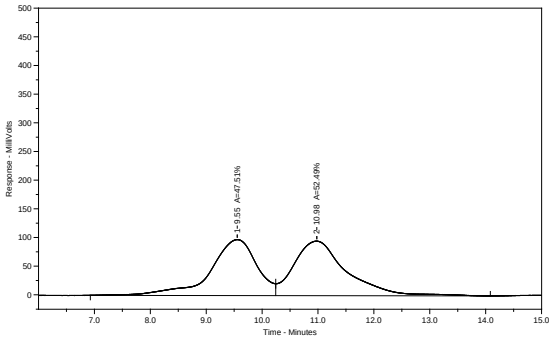
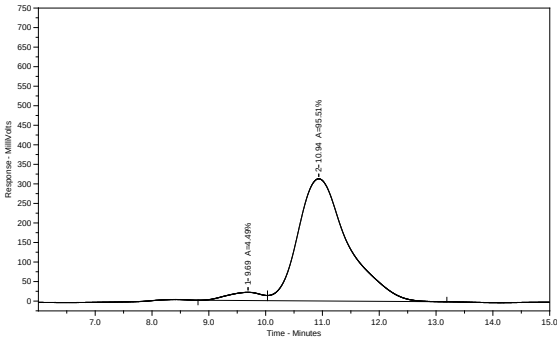
6.5 Hz, b or b'), 39.83 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 32.73 (d, $^{3}J_{C\text{-}P}$ = 14.0 Hz, e), 16.50 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.26 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.65 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.79 ppm; IR (neat) 3395 (O-H), 2981 (sp^2 C-H), 2932 (sp^3 C-H), 1602, 1508 (C-F), 1444 (aromatic C=C), 1392 (aromatic C=C), 1219 (P=O), 1021 (C-O), 960 (P-O), 836 cm^{-1}. HRMS (ESI) calculated for $C_{13}H_{20}FO_4P+Na^+$ = 313.0981, found 313.0992 *m/z*. Enantiomer ratio = 96:4, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile phase = Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

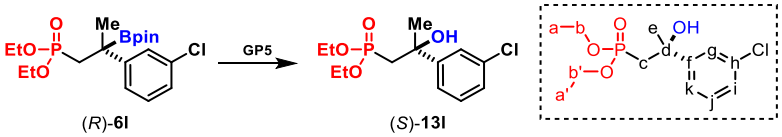
(a) **13j** Racemate	(b) R:S = 96:4, CAHB of **5j** with (*S*,*S*)-**T2**, then oxidation to yield **13j**.
	



Synthesis of chiral tertiary benzyl alcohol (*S*)-13k: Following **GP5**, the chiral boronic ester (*R*)-**6k** (42 mg, 0.10 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13k** (29 mg, 95%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = -5.7° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (2H, d, *J* = 8.5 Hz, h),

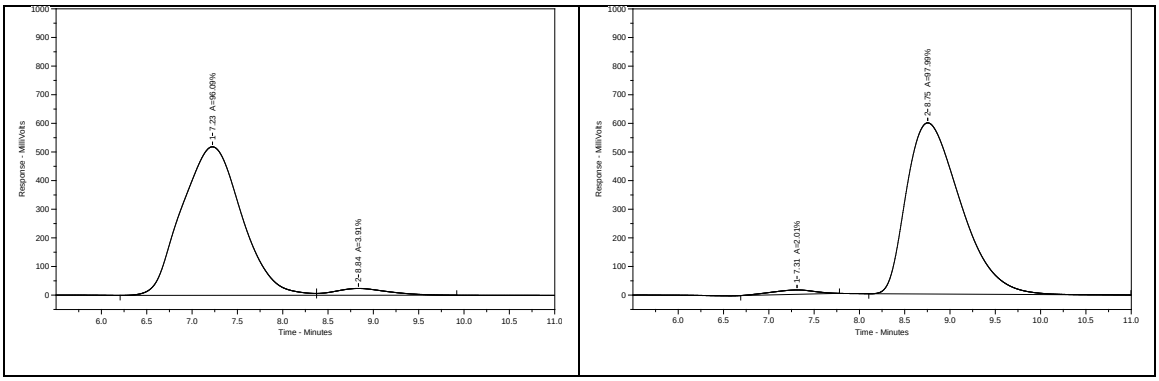
7.31 (2H, d, *J* = 8.5 Hz, g), 5.06 (1H, s, OH), 4.14-4.00 (2H, m, b or b'), 3.81-3.72 (1H, m, b or b'), 3.58-3.48 (1H, m, b or b'), 2.42 (1H, dd, *J* = 18.0, 15.0 Hz, c(1H)), 2.32 (1H, dd, *J* = 18.0, 15.0 Hz, c(1H)), 1.60 (3H, d, $^{4}J_{C\text{-}P}$ = 2.5 Hz, e), 1.32 (3H, t, *J* = 7.0 Hz, a or a'), 1.05 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.01 (d, $^{3}J_{C\text{-}P}$ = 7.5 Hz, f), 131.74 (i), 127.32 (g), 125.56 (h), 70.91 (d, $^{2}J_{C\text{-}P}$ = 5.0 Hz, d), 60.99 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 60.82 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 38.66 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 31.55 (d, $^{3}J_{C\text{-}P}$ = 14.0 Hz, e), 15.51 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 15.23 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.52 ppm; IR (neat) 3382 (O-H), 2979 (sp^2 C-H), 2929 (sp^3 C-H), 1489 (aromatic C=C), 1391 (aromatic C=C), 1215 (P=O), 1022 (C-O), 961 (P-O), 831 (C-Cl) cm^{-1}. HRMS (ESI) calculated for $C_{13}H_{20}ClO_4P+Na^+$ = 329.0685, found 329.0693 *m/z*. Enantiomer ratio = 96:4, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IA; Mobile phase = 95:5 Hexanes: Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

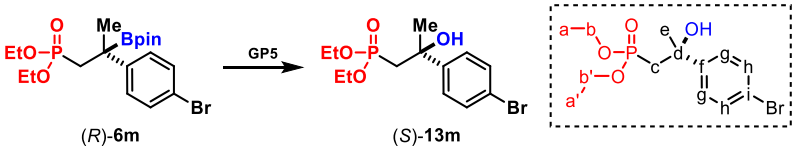
(a) **13k** Racemate	(b) R:S = 96:4, CAHB of **5k** with (*S*,*S*)-**T2**, then oxidation to yield **13k**.
	



Synthesis of chiral tertiary benzyl alcohol (*S*)-13l: Following **GP5**, the chiral boronic ester (*R*)-**6l** (42 mg, 0.10 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13l** (27 mg, 88%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = -5.7° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, t, *J* = 2.0 Hz, aryl), 7.37 (1H, dt, *J* = 7.5, 1.5 Hz, aryl), 7.27 (1H, t, *J* = 7.5 Hz, aryl), 7.22 (1H, dt, *J* = 7.5, 1.5 Hz, aryl), 5.07 (1H, br s, OH), 4.14-3.99 (2H, m, b or b'), 3.82-3.71 (1H, m, b or b'), 3.59-3.49 (1H, m, b or b'), 2.43 (1H, dd, *J* = 18.0, 15.0 Hz, c(1H)), 2.31 (1H, dd, *J* = 18.0, 15.0 Hz, c(1H)), 1.60 (3H, d, $^4J_{P\text{-}H}$ = 2.5 Hz, e), 1.32 (3H, t, *J* = 7.0 Hz, a or a'), 1.05 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.63 (d, $^3J_{C\text{-}P}$ = 7.5 Hz, f), 134.25 (h), 129.59 (aryl), 127.03 (aryl), 125.47 (aryl), 123.23 (aryl), 71.90 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 61.99 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.82 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 39.51 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 32.51 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, e), 16.49 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.36 ppm; IR (neat) 3370 (O-H), 2980 (sp^2 C-H), 2931 (sp^3 C-H), 1596, 1571, 1475 (aromatic C=C), 1392 (aromatic C=C), 1215 (P=O), 1020 (C-O), 960 (P-O), 738 (C-Cl) cm^{-1}. HRMS (ESI) calculated for $C_{13}H_{20}ClO_4P$+Na^+ = 329.0685, found 329.0688 *m/z*. Enantiomer ratio = 97:3, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AS-H; Mobile phase = 90:10 Hexanes:Isopropanol; Flow rate = 1.25 mL/min. HPLC UV detector λ = 220 nm, rt. HPLC traces:

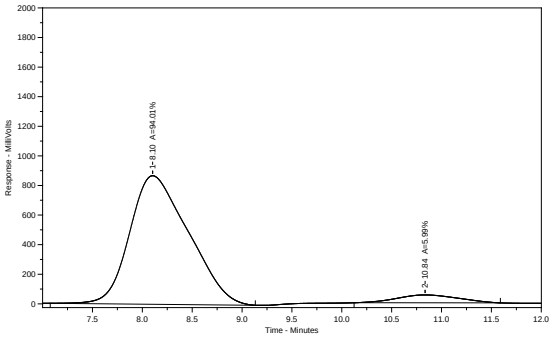
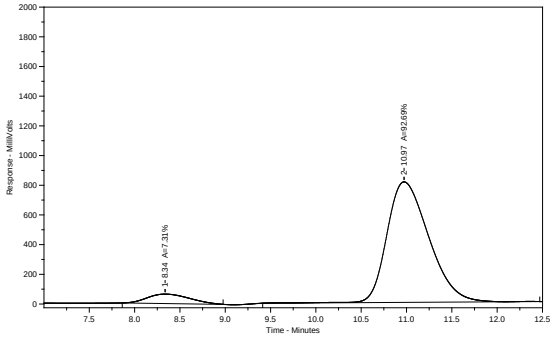
(a) R:S = 4:96, CAHB of **5l** with (*R*,*R*)-**T2**, then oxidation to yield **13l**:	(b) R:S = 98:2, CAHB of **5l** with (*S*,*S*)-**T2**, then oxidation to yield **13l**:

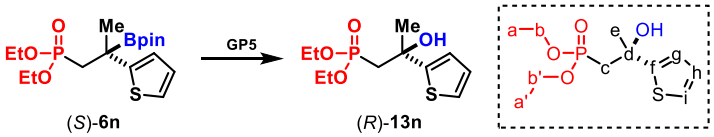




Synthesis of chiral tertiary benzyl alcohol (*S*)-13m: Following **GP5**, the chiral boronic ester (*R*)-**6m** (46 mg, 0.1 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13m** (28 mg, 81%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = -1.3° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (2H, d, *J* = 8.5 Hz, h), 7.37 (2H, d, *J* = 8.5 Hz, g), 5.05 (1H, br s, OH), 4.14-4.00 (2H, m, b or b'), 3.82-3.72 (1H, m, b or b'), 3.59-3.49 (1H, m, b or b'), 2.42 (1H, dd, *J* = 18.0, 15.0 Hz, c(1H)), 2.31 (1H, dd, *J* = 18.0, 15.0 Hz, c(1H)), 1.60 (3H, d, $^4J_{C\text{-}P}$ = 2.0 Hz, e), 1.33 (3H, t, *J* = 7.0 Hz, a or a'), 1.05 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.55 (d, $^3J_{C\text{-}P}$ = 7.5 Hz, f), 131.29 (h), 126.95 (g), 120.86 (i), 71.96 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 62.01 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.84 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 39.62 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 32.51 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, e), 16.52 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.23 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.49 ppm; IR (neat) 3391 (O-H), 2980 (sp^2 C-H), 2931 (sp^3 C-H), 1590, 1486 (aromatic C=C), 1393 (aromatic C=C), 1214 (P=O), 1021 (C-O), 960 (P-O), 828, 731 (C-Br) cm^{-1}. HRMS (ESI) calculated for $C_{13}H_{20}BrO_4P+Na^+$ = 375.0160,

found 375.0173 *m/z*. Enantiomer ratio = 94:6, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AS-H; Mobile phase = 90:10 Hexanes:Isopropanol; Flow rate = 1.25 mL/min. HPLC UV detector λ = 220 nm, rt. HPLC traces:

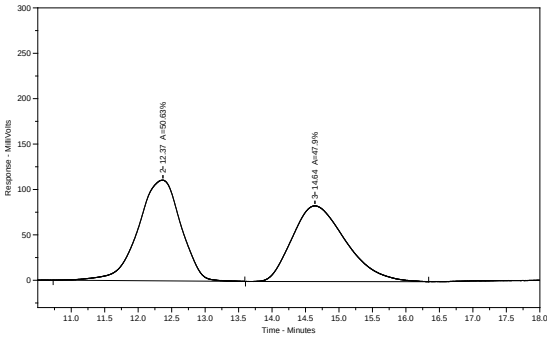
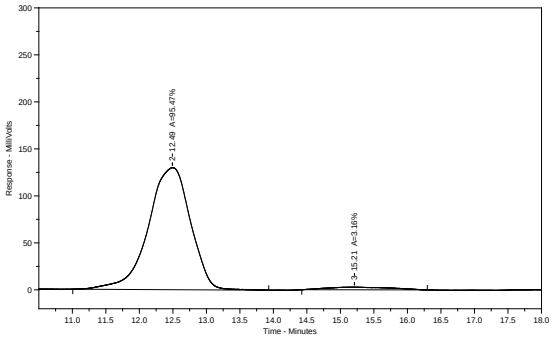
(a) R:S = 6:94, CAHB of **5m** with (*R*,*R*)-**T2**, then oxidation to yield **13m**:	(b) R:S = 93:7, CAHB of **5m** with (*S*,*S*)-**T2**, then oxidation to yield **13m**:
	

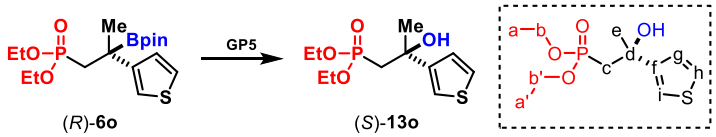


(*S*)-**6n** (*R*)-**13n**

Synthesis of chiral tertiary benzyl alcohol (*R*)-13n: Following **GP5**, the chiral boronic ester (*S*)-**6n** (39 mg, 0.1 mmol) yields the chiral tertiary β-hydroxyphosphonate (*R*)-**13n** (23 mg, 83%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; $[\alpha]_D^{20}$ = +16° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, dd, *J* = 4.0, 2.0 Hz, i), 6.96-6.94 (2H, m, g+h), 5.29 (1H, br s, OH), 4.15-4.05 (2H, m b or b'), 3.94-3.84 (1H, m, b or b'), 3.73-3.63 (1H, m, b or b'), 2.50 (1H, dd, *J* = 18.0, 15.0 Hz, c(1H)), 2.39 (1H, dd, *J* = 18.0, 15.0 Hz, c(1H)), 1.73 (3H, d, $^4J_{P\text{-}H}$ = 2.0 Hz, e), 1.34 (3H, t, *J* = 7.0 Hz, a or a'), 1.16 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.07 (d, $^3J_{C\text{-}P}$ = 10.0 Hz, f), 126.84 (g or h), 124.12 (i), 122.54 (g or h), 71.45 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d),

62.22 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.77 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 40.73 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 33.36 (d, $^{3}J_{C\text{-}P}$ = 12.5 Hz, e), 16.52 (d, $^{3}J_{C\text{-}P}$ = 6.5 Hz, a or a'), 16.40 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.09 ppm; IR (neat) 3367 (O-H), 2980 (sp^2 C-H), 2930 (sp^3 C-H), 1442 (aromatic C=C), 1391 (aromatic C=C), 1214 (P=O), 1018 (C-O), 959 (P-O), 836, 695 cm^{-1}. HRMS (ESI) calculated for $C_{11}H_{19}O_4PS+Na^+$ = 301.0639, found 301.0644 *m/z*. Enantiomer ratio = 97:3, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AS-H; Mobile phase = 90:10 Hexanes:Isopropanol; Flow rate = 1.25 mL/min. HPLC UV detector λ = 220 nm, rt. HPLC traces:

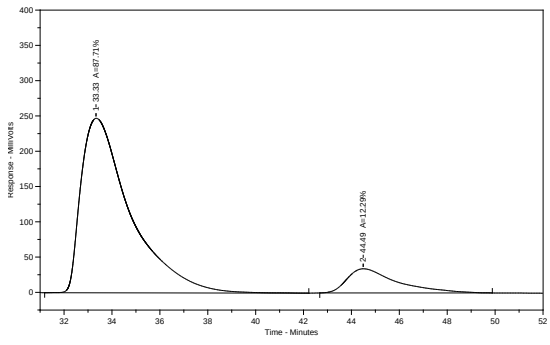
(a) **13n** Racemate	(b) R:S = 7:93, CAHB of **5n** with (*S*,*S*)-**T2**, then oxidation to yield **13n**.
	



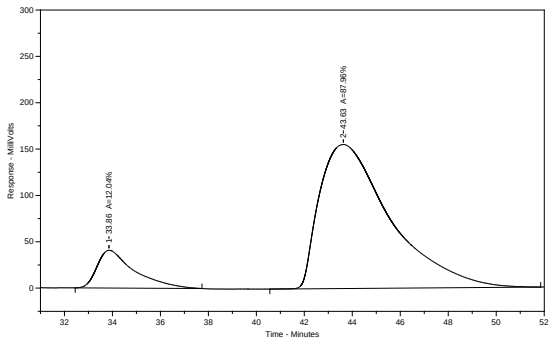
Synthesis of chiral tertiary benzyl alcohol (*S*)-13o: Following **GP5**, the chiral boronic ester (*R*)-**6o** (39 mg, 0.1 mmol) yields the chiral tertiary β-hydroxyphosphonate (*S*)-**13o** (24 mg, 87%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 2:1) R_f = 0.5; $[\alpha]_D^{20}$ = -11.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (1H, dd, *J* = 4.0, 2.0

Hz, h), 7.28-7.26 (2H, m, g+i), 5.04 (1H, br s, OH), 4.14-4.00 (2H, m b or b'), 3.87-3.77 (1H, m, b or b'), 3.62-3.52 (1H, m, b or b'), 2.42 (1H, dd, J = 18.0, 15.0 Hz, c(1H)), 2.32 (1H, dd, J = 18.0, 15.0 Hz, c(1H)), 1.62 (3H, d, $^{4}J_{P\text{-}H}$ = 2.0 Hz, e), 1.32 (3H, t, J = 7.0 Hz, a or a'), 1.11 (3H, t, J = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.48 (d, $^{3}J_{C\text{-}P}$ = 8.0 Hz, f), 125.91 (g or i), 125.68 (g or i), 120.04 (h), 71.17 (d, $^{2}J_{C\text{-}P}$ = 5.0 Hz, d), 61.98 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.66 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 39.89 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 32.27 (d, $^{3}J_{C\text{-}P}$ = 14.0 Hz, e), 16.51 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.38 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.66 ppm; IR (neat) 3391 (O-H), 2978 (sp^2 C-H), 2922 (sp^3 C-H), 1443 (aromatic C=C), 1392 (aromatic C=C), 1221 (P=O), 1020 (C-O), 960 (P-O), 790 cm^{-1}. HRMS (ESI) calculated for $C_{11}H_{19}O_4PS+Na^+$ = 301.0639, found 301.0646 *m/z*. Enantiomer ratio = 88:12, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile phase = 90:10 Hexanes: Isopropanol; Flow rate = 1.5 mL/min. HPLC UV detector λ = 220 nm, rt. HPLC traces:

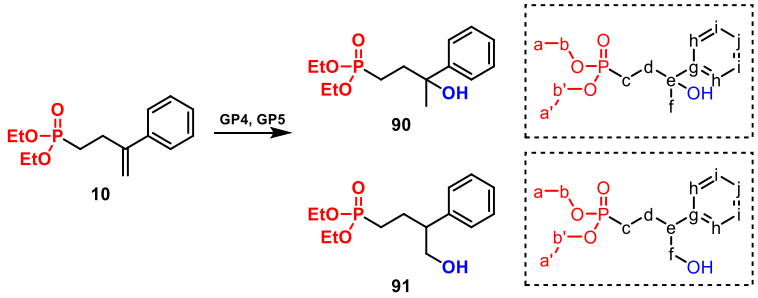
(a) R:S = 12:88, CAHB of **5o** with (*R*,*R*)-**T2**, then oxidation to yield **13o**:



(b) R:S = 88:12, CAHB of **5o** with (*S*,*S*)-**T2**, then oxidation to yield **13o**:



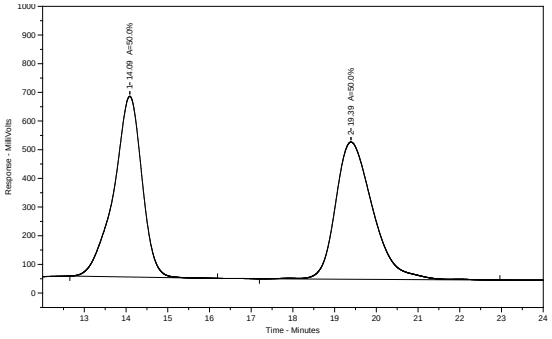
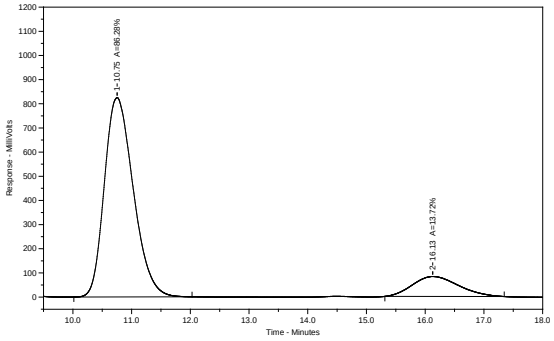
Synthesis of chiral primary alcohol (*S*)-**101:** See sec. 5.11.3 CAHB of non-conjugated methylidene substrate 7.



Synthesis of chiral alcohols 35 & 36: Following the general procedure for CAHB (**GP4**; 12 h total reaction time), the substrate **10** (54 mg, 0.2 mmol) yields about a 1:1 mixture of regioisomeric boronic esters (tertiary boronic ester **11** and primary boronic ester **12**) that were not separable. The crude CAHB mixture was chromatographed (ethyl acetate/hexanes 1:1) over silica gel to get rid of the non-polar colored complex and the polar metal residues. The crude mixture obtained after this partial purification is subjected to oxidation following **GP5** to obtain the corresponding alcohols that were separated and purified by silica gel chromatography.

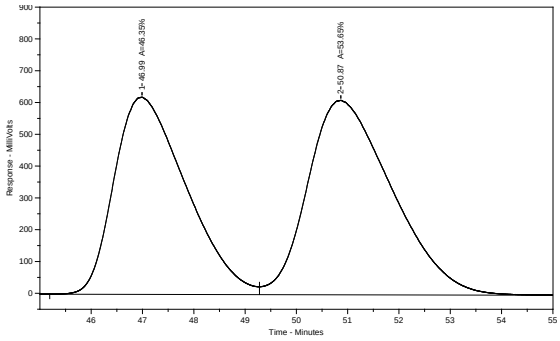
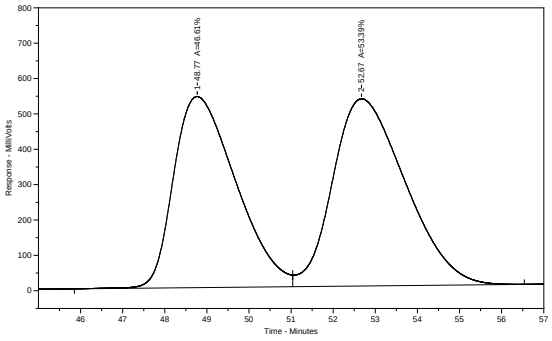
The tertiary alcohol **90** is obtained as a colorless oil (23 mg, 40%): TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +1.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.44 (2H, d, *J* = 8.0 Hz, h), 7.36 (2H, dd, *J* = 8.0, 7.5 Hz, i), 7.26 (1H, t, *J* = 7.5 Hz, j), 4.12-4.02 (4H, m, b+b'), 2.80 (1H, br s, OH), 2.18-2.08 (2H, m, d), 1.79-1.72 (1H, m, c(1H)), 1.62-1.55 (4H, m, c(1H)+f), 1.32 (3H, t, *J* = 7.0 Hz, a or a'), 1.29 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 146.92 (g), 128.52 (i), 126.94 (j), 125.04 (h), 74.21 (d, $^3J_{C\text{-}P}$ = 13.5 Hz, e), 61.87 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 36.65 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, d), 30.97 (f), 20.76 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.64 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a or a'), 16.60 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a or a') ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 33.68 ppm; IR (neat) 3361 (O-H), 3025 (aromatic C-H), 2931 (aliphatic C-H), 1446 (aromatic C=C), 1392 (aromatic C=C),

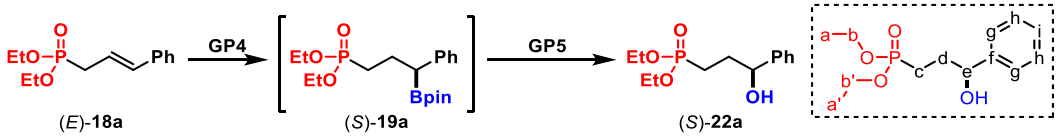
1219 (P=O), 1052 (C-O), 1021 (C-O), 960 (P-O) 700 cm^{-1}; Enantiomer ratio = 86:14, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AS-H; Mobile Phase = 40:60 Hexanes:Isopropanol. Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a) Racemate	(b) Er = 86:14, CAHB of **10** with (*S,S*)-**T2**, then oxidation to yield **90**.
	

The primary alcohol **91** is obtained as a colorless oil (24 mg, 41%): TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -1.6° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.21 (5H, m, aryl), 4.13-4.00 (4H, m, b+b'), 3.78 (2H, br t, *J* = 5.0 Hz, f), 2.88-2.81 (1H, m, e), 2.16-2.05 (1H, m, d(1H)), 1.95-1.84 (1H, m, d(1H)), 1.76 (1H, br s, OH), 1.70-1.56 (2H, m, c), 1.31 (3H, t, *J* = 7.0 Hz, a or a'), 1.30 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.18 (g), 129.04 (h or i), 128.25 (h or i), 127.31 (j), 67.27 (f), 61.71 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b+b'), 49.34 (d, $^3J_{C\text{-}P}$ = 16 Hz, e), 24.98 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 23.75 (d, $^1J_{C\text{-}P}$ = 141 Hz, c), 16.65 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.17 ppm; IR (neat) 3363 (O-H), 2989 (aromatic C-H), 2930 (aliphatic C-H), 1447 (aromatic C=C), 1389 (aromatic C=C), 1220 (P=O), 1052 (C-O), 1021 (C-O), 963 (P-O) 702 cm^{-1}; Enantiomer ratio = 46:54, determined by chiral HPLC analysis: Stationary phase =

CHIRALPAK IC; Mobile Phase = 30:70 Hexanes:Isopropanol. Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

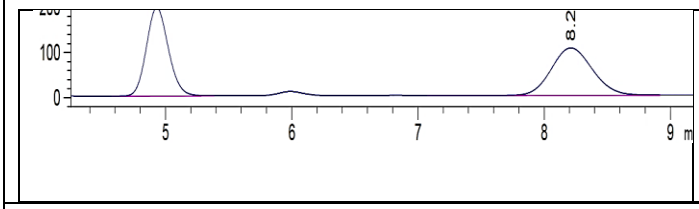
(a) Er = 54:46, CAHB of **10** with (*R*,*R*)-**T2**, then oxidation to yield **91**:	(b) Er = 53:47, CAHB of **10** with (*S*,*S*)-**T2**, then oxidation to yield **91**:
	



Preparation of chiral secondary benzylic alcohol (*S*)-22a: Following the general procedure for sequential hydroboration-oxidation (**GP4**/**GP5**), the substrate (*E*/*Z*)-**18a** (76 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22a** (67 mg, 82%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.2; $[\alpha]_D^{20}$ = -29.1° (*c* = 1.0, $CHCl_3$) [**Absolute Configuration Assignment:** *Alcohol **22a** is a previously reported[13] compound in the literature and the negative value of optical rotation obtained for **22a** is expected for the (S)-enantiomer.*]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (5H, m, aryl), 4.80 (1H, dd, *J* = 6.5, 6.0 Hz, e), 4.15-4.06 (4H, m, b+b'), 2.87 (1H, br s, OH), 2.09-2.04 (2H, m, d), 1.94-1.79 (2H, m, c), 1.33 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 144.04 (f), 128.69 (g or h), 127.82 (i), 125.96 (g or h), 74.02 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 61.89

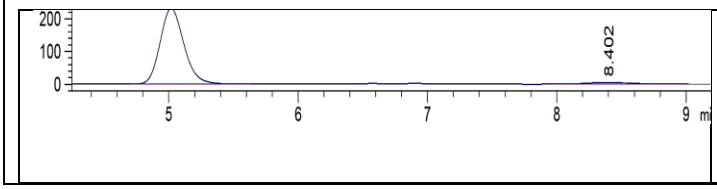
(d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 61.86 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 31.99 (d, $^{2}J_{C\text{-}P}$ = 5.0 Hz, d), 22.15 (d, $^{1}J_{C\text{-}P}$ = 142 Hz, c), 16.63 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 32.83 ppm; IR (neat) 3369 (O-H), 3026 (sp^2 C-H), 2928 (sp^3 C-H), 1493 (aromatic C=C), 1452 (aromatic C=C), 1392 (aromatic C=C), 1225 (P=O), 1053 (C-O), 1021 (C-O), 956 (P-O), 700 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{21}O_4P+Na^+$ = 295.1075, found 295.1081 *m/z*. Enantiomer ratio = 96:4, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1.0 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate:

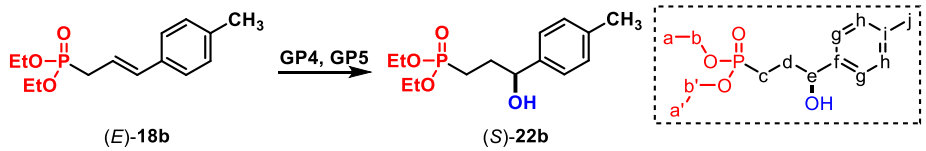


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.930	BB	0.1873	2383.36279	50.0002
2	8.210	VB	0.3529	2383.34546	49.9998

(b) R:S = 4:96, CAHB of (*E*/Z)-**18a** using (*R*)-**B2** followed by oxidation:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.018	BB	0.1972	2961.21484	95.7663
2	8.402	BB	0.3608	130.91283	4.2337

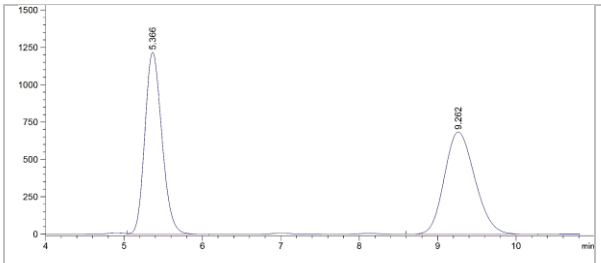


(*E*)-**18b** (*S*)-**22b**

Preparation of chiral secondary benzylic alcohol (*S*)-22b: Following the general procedure for sequential hydroboration-oxidation (**GP4**/**GP5**), the substrate (*E*)-**18b** (81 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22b** (72 mg, 84%) as a colorless oil: TLC analysis (2% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -37° (*c* = 1.0,

$CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (2H, d, *J* = 8.0 Hz, g), 7.13 (2H, d, *J* = 8.0 Hz, h), 4.67 (1H, t, *J* = 6.0 Hz, e), 4.11-3.95 (4H, m, b+b'), 3.57 (1H, br s, OH), 2.32 (3H, s, j), 2.04-1.92 (2H, m, d), 1.90-1.67 (2H, m, c), 1.28 (3H, t, *J* = 7.0 Hz, a or a'), 1.27 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.26 (f), 137.12 (i), 129.14 (h), 125.88 (g), 73.52 (d, $^3J_{C\text{-}P}$ = 16 Hz, e), 61.71 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.68 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 31.86 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 21.96 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 21.18 (j), 16.51 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.93 ppm; IR (neat) 3358 (O-H), 2981 (aromatic C-H), 2927 (aliphatic C-H), 1513 (aromatic C=C), 1441 (aromatic C=C), 1392 (aromatic C=C), 1226 (P=O), 1058 (C-O), 1019 (C-O), 954 (P-O), 816, 524 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_4P+Na^+$ = 309.1232, found 309.1242 *m/z*. Enantiomer ratio = 97:3, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

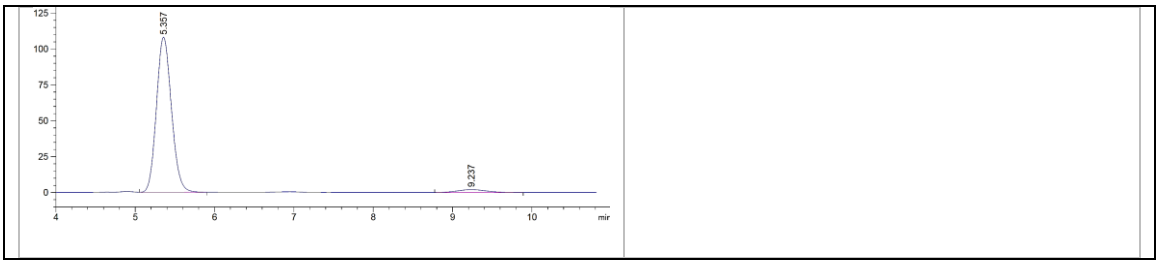
(a) Racemate:

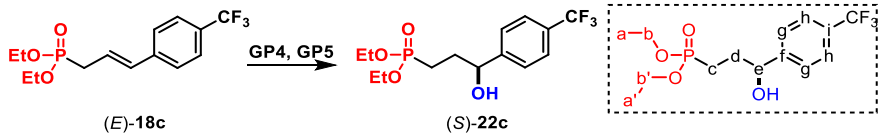


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.366	VB	0.2350	1.83563e4	49.9344
2	9.262	VB	0.4214	1.84046e4	50.0656

(b) R:S = 3:97, CAHB of (*E*)-**18b** using (*R*)-**B2** followed by oxidation to yield (*S*)-**9b**:

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.357	VB	0.2048	1425.46387	96.5603
2	9.237	BB	0.3767	50.77775	3.4397



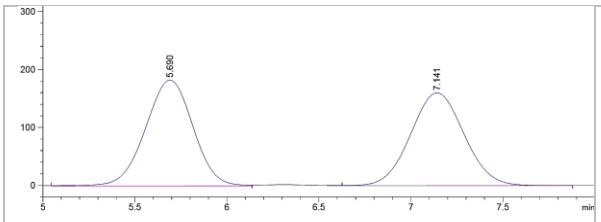


(*E*)-**18c** (*S*)-**22c**

Preparation of chiral secondary benzylic alcohol (*S*)-22c: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18c** (81.0 mg, 0.25 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22c** (67 mg, 78%) as a colorless oil: TLC analysis (1% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -22° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* = 8.2 Hz, h), 7.46 (2H, d, *J* = 8.2 Hz, g), 4.81 (1H, t, *J* = 6.0 Hz, e), 4.30 (1H, br s, OH), 4.11-3.96 (4H, m, b+b'), 2.08-1.75 (4H, m, c+d), 1.28 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.49 (f), 129.70 (q, $^2J_{C\text{-}F}$ = 32.31 Hz, i), 126.27 (g), 125.45 (q, $^3J_{C\text{-}F}$ = 4.0 Hz, h), 124.33 (q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3), 72.88 (d, $^3J_{C\text{-}P}$ = 14 Hz, e), 61.99 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.94 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 32.06 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 21.83 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.53 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.64 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.48 ppm; IR (neat) 3332 (O-H), 2986 (aromatic C-H), 2932 (aliphatic C-H), 1442 (aromatic C=C), 1413 (aromatic C=C), 1323 (C-F), 1226 (P=O), 1161, 1120, 1064 (C-O), 1016 (C-O), 959 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{20}F_3O_4P$+Na^+ = 363.0949, found 363.0950 *m/z*; Enantiomer ratio = 97:3, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 20:80

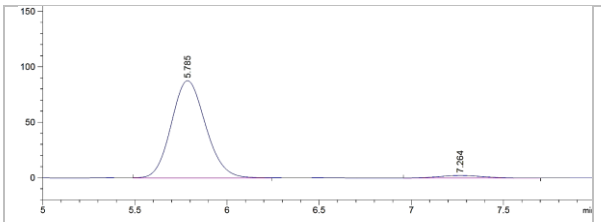
Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 ºC. HPLC traces:

(a) Racemate:

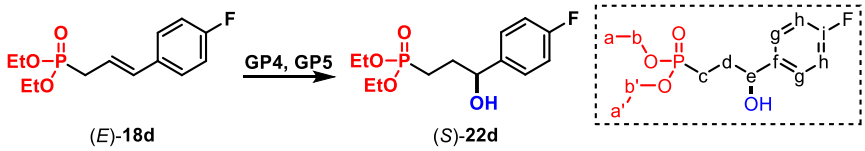


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.690	VV	0.2817	3299.05396	50.3856
2	7.141	VB	0.3156	3248.56299	49.6144

(b) R:S = 3:97, CAHB of (*E*)-**18c** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22c**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.785	VB	0.2017	1140.88721	96.7109
2	7.264	BB	0.2570	38.80151	3.2891

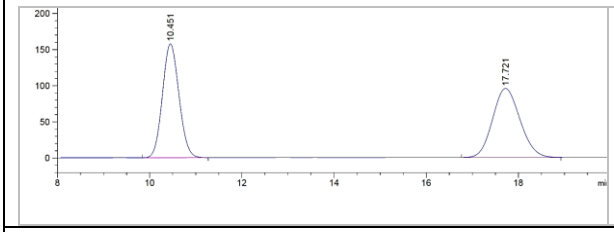


(*E*)-**18d** (*S*)-**22d**

Preparation of chiral secondary benzylic alcohol (*S*)-22d: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18d** (82 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22d** (62 mg, 71%) as a colorless oil: TLC analysis (1% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -34º (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (2H, m, g), 7.02-6.97 (2H, m, h), 4.70 (1H, t, *J* = 6.0 Hz, e), 4.11-3.95 (4H, m, b+b'), 3.91 (1H, br s, OH), 2.02-1.90 (2H, m, d), 1.88-1.67 (2H, m, c), 1.28 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.21 (d, $^1J_{C\text{-}F}$ = 245 Hz, i), 140.11 (d, $^4J_{C\text{-}P}$ = 3.0 Hz, f), 127.57 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, g),

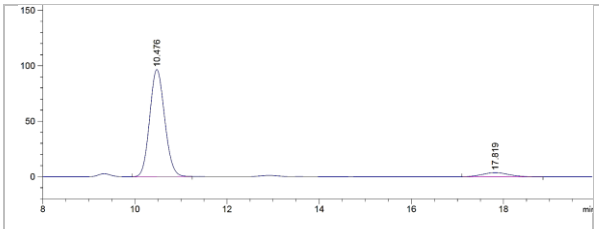
115.28 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz, h), 72.97 (d, $^{3}J_{C\text{-}P}$ = 15.25 Hz, e), 61.85 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.82 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 32.07 (d, $^{2}J_{C\text{-}P}$ = 4.5 Hz, d), 21.94 (d, $^{1}J_{C\text{-}P}$ = 142 Hz, c), 16.54 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.75 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.41 ppm; IR (neat) 3356 (O-H), 2982 (aromatic C-H), 2931 (aliphatic C-H), 1508 (C-F), 1218 (P=O), 1054 (C-O), 1021 (C-O), 957 (P-O), 833 cm^{-1}; HRMS (ESI) calculated for $C_{13}H_{20}FO_4P+Na^{+}$ = 313.0981, found 313.0983 *m/z*; Enantiomer ratio = 94:6, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 20:80 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate:

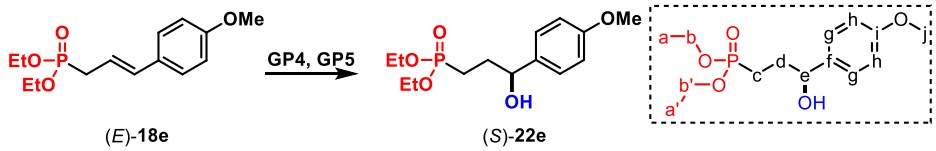


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	10.451	BB	0.3889	3926.03564	49.8717
2	17.721	BB	0.6473	3946.23096	50.1283

(b) R:S = 6:94, CAHB of (*E*)-**18d** using (*R*)-**B1** followed by oxidation to yield (*S*)-**22d**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	10.476	BB	0.3517	2183.74219	93.6814
2	17.819	BB	0.5782	147.28763	6.3186

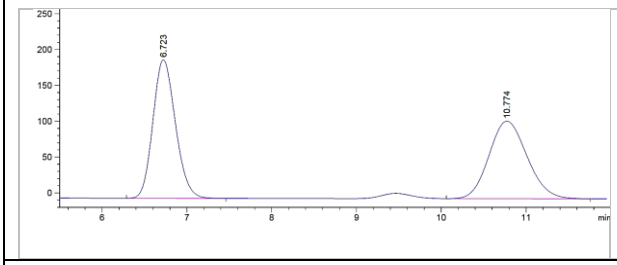


(*E*)-**18e** (*S*)-**22e**

Preparation of chiral secondary benzylic alcohol (*S*)-22e: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18e** (85

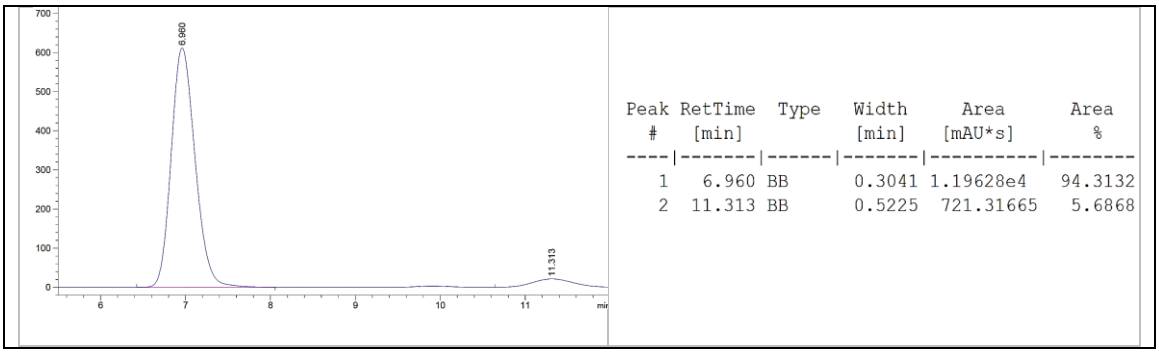
mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22e** (70 mg, 77%) as a colorless oil: TLC analysis (3% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -26° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.5 Hz, g), 6.88 (2H, d, *J* = 8.5 Hz, h), 4.70 (1H, t, *J* = 6.25 Hz, e), 4.14-3.99 (4H, m, b+b'), 3.81 (3H, s, j), 3.05 (1H, br s, OH), 2.09-1.94 (2H, m, d), 1.93-1.69 (2H, m, c), 1.31 (6H, t, *J* = 3.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.22 (i), 136.27 (f), 127.21 (g), 114.01 (h), 73.57 (d, $^3J_{C\text{-}P}$ = 15.5 Hz, e), 61.83 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.80 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 55.46 (j), 31.96 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 22.15 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.61 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.85 ppm; IR (neat) 3361 (O-H), 2982 (aromatic C-H), 2836 (aliphatic C-H), 1511, 1442 (aromatic C=C), 1392 (aromatic C=C), 1241 (P=O), 1020 (C-O), 956 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_5P+Na^+$ = 325.1181, found 325.1183 *m/z*; Enantiomer ratio = 94:6, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1.5 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate:

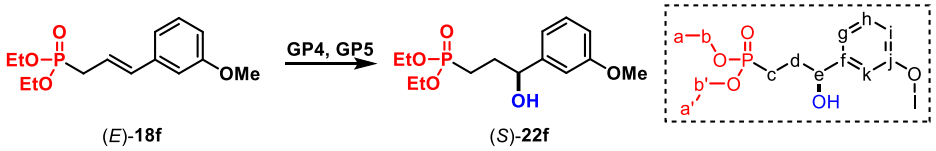


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	6.723	BB	0.2864	3569.89966	51.3988
2	10.774	VB	0.4850	3375.58862	48.6012

(b) R:S = 6:94, CAHB of (*E*)-**18e** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22e**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	6.960	BB	0.3041	1.19628e4	94.3132
2	11.313	BB	0.5225	721.31665	5.6868

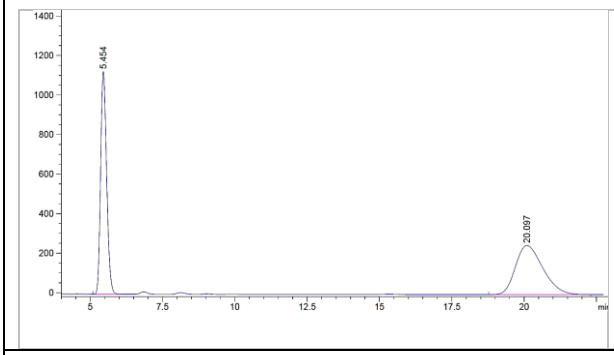


(*E*)-**18f** (*S*)-**22f**

Preparation of chiral secondary benzylic alcohol (*S*)-22f: Following the general procedure for sequential hydroboration-oxidation (**GP4**/**GP5**), the substrate (*E*)-**18f** (85 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22f** (76 mg, 83%) as a colorless oil: TLC analysis (3% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -21° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (1H, dd, *J* = 8.25, 7.68 Hz, h), 6.93-6.91 (2H, m, g+k), 6.82-6.79 (1H, m, i), 4.73 (1H, t, *J* = 6.0 Hz, e), 4.13-3.99 (4H, m, b+b'), 3.81 (3H, s, l), 3.33 (1H, br s, OH), 2.08-1.95 (2H, m, d), 1.93-1.72 (2H, m, c), 1.30 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.92 (j), 149.91 (f), 129.63 (h), 118.29 (g), 113.17 (i), 111.45 (k), 73.74 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 61.86 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.82 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 55.39 (l), 31.94 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 22.02 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.60 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.87 ppm; IR (neat) 3352 (O-H), 2982 (aromatic C-H), 2837 (aliphatic C-H), 1600, 1486 (aromatic C=C), 1436 (aromatic C=C), 1226 (P=O), 1020 (C-O), 957 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_5P$+Na^+ = 325.1181, found 325.1184 *m/z*. Enantiomer ratio = 98:2, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase

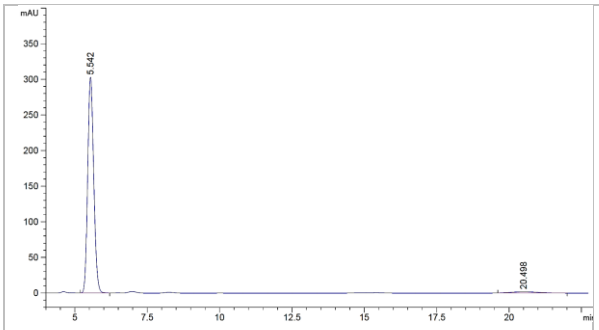
= 50:50 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 ^{o}C. HPLC traces:

(a) Racemate

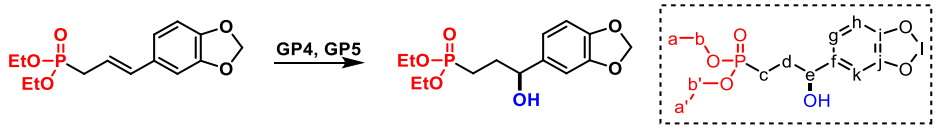


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.454	VB	0.2230	1.62339e4	49.7841
2	20.097	BB	1.0219	1.63747e4	50.2159

(b) R:S = 2:98, CAHB of (*E*)-**18f** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22f**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.542	BB	0.2244	4372.33838	97.5272
2	20.498	BB	0.7239	110.86235	2.4728

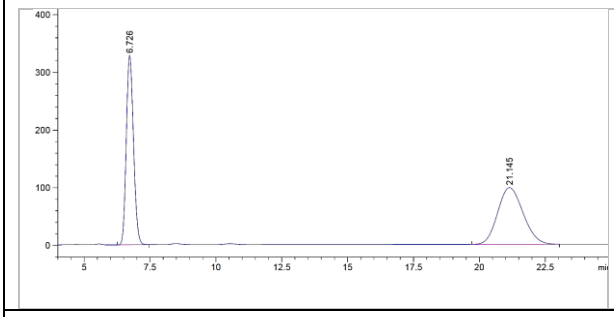


(*E*)-**18g** (*S*)-**22g**

Preparation of chiral secondary benzylic alcohol (*S*)-22g: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18g** (75.0 mg, 0.25 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22g** (55 mg, 70%) as a colorless oil: TLC analysis (5% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -39^{o} (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (1H, d, *J* = 1.25 Hz, k), 6.77-6.71 (2H, m,

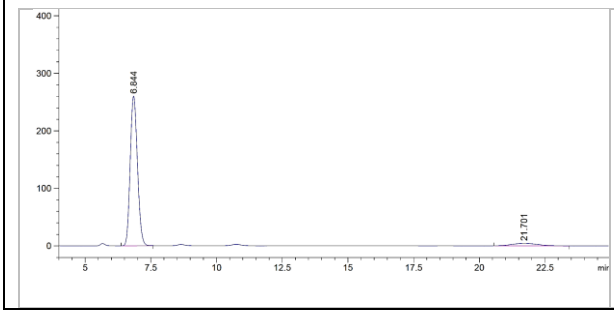
g+h), 5.92 (2H, s, l), 4.62 (1H, t, *J* = 6.0 Hz, e), 4.13-4.96 (4H, m, b+b'), 3.62 (1H, br s, OH), 2.02-1.62 (4H, m, c+d), 1.28 (3H, t, *J* = 7.0 Hz, a or a'), 1.27 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.85 (i or j), 146.93 (i or j), 138.38 (f), 119.30 (g), 108.13 (h), 106.48 (k), 101.06 (l), 73.54 (d, $^{3}J_{C\text{-}P}$ = 16 Hz, e), 61.79 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.75 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 31.96 (d, $^{2}J_{C\text{-}P}$ = 4.5 Hz, d), 21.99 (d, $^{1}J_{C\text{-}P}$ = 142 Hz, c), 16.54 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.81 ppm; IR (neat) 3336 (O-H), 2982 (aromatic C-H), 2903 (aliphatic C-H), 1486 (aromatic C=C), 1440 (aromatic C=C), 1234 (P=O), 1020 (C-O), 957 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{21}O_6P$+Na^+ = 339.0973, found 339.0975 *m/z*; Enantiomer ratio = 94:6, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate:

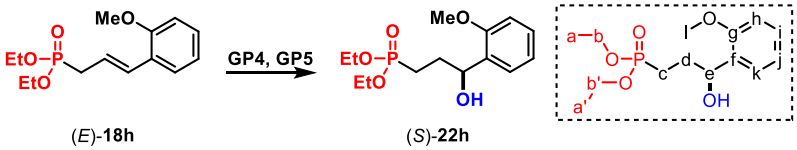


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	6.726	BB	0.2981	6244.61572	48.5713
2	21.145	BB	1.0529	6611.98193	51.4287

(b) R:S = 6:94, CAHB of (*E*)-**18g** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22g**



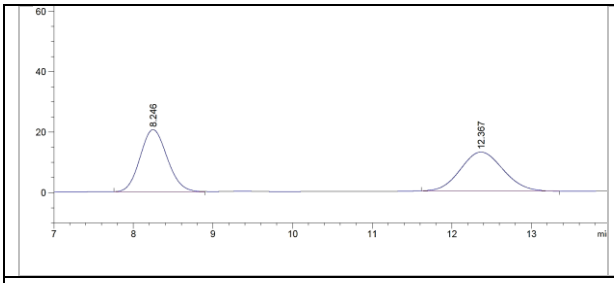
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	6.844	BB	0.2993	4980.82617	94.4086
2	21.701	BB	0.8190	294.99234	5.5914



(*E*)-**18h** (*S*)-**22h**

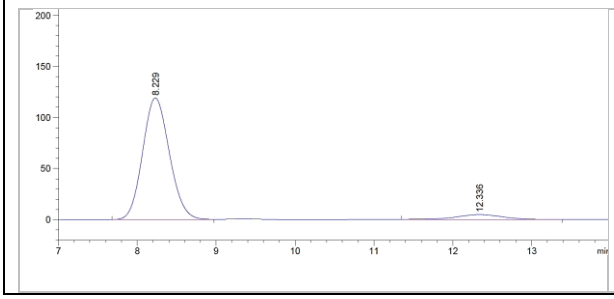
Preparation of chiral secondary benzylic alcohol (*S*)-22h: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**; Note: CAHB carried out for 12 hours), the substrate (*E*)-**18h** (71.0 mg, 0.25 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22h** (54 mg, 72%) as a colorless oil: TLC analysis (4% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -29° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, dd, *J* = 7.5, 1.5 Hz, aryl), 7.23 (1H, td, *J* = 8.0, 1.5 Hz), 6.95 (1H, td, *J* = 7.5, 1.0 Hz, aryl), 6.85 (1H, d, *J* = 8.25 Hz, aryl), 4.93 (1H, t, *J* = 6.0 Hz, e), 4.15-3.99 (4H, m, b+b'), 3.82 (3H, s, l), 3.41 (1H, br s, OH), 2.12-1.71 (4H, m, c+d), 1.30 (3H, t, *J* = 7.0 Hz, a or a'), 1.29 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.37 (g), 131.85 (f), 128.47 (aryl), 126.97 (aryl), 120.84 (aryl), 110.50 (aryl), 70.09 (d, $^3J_{C\text{-}P}$ = 17 Hz, e), 61.67 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 55.34 (l), 30.05 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 22.17 (d, $^1J_{C\text{-}P}$ = 141 Hz, c), 16.55 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.22 ppm; IR (neat) 3367 (O-H), 2981 (aromatic C-H), 2907 (aliphatic C-H), 1489 (aromatic C=C), 1464 (aromatic C=C), 1439 (aromatic C=C), 1235 (P=O), 1048 (C-O), 1022 (C-O), 957 (P-O), 754, 729 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_5P+Na^+$ = 325.1181, found 325.1183 *m/z*; Enantiomer ratio = 94:6, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate

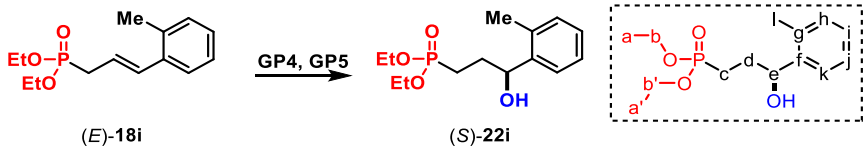


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.246	BB	0.3683	485.50961	50.2144
2	12.367	BB	0.5805	481.36310	49.7856

(b) R:S = 6:94, CAHB of (*E*)-**18h** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22h**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.229	BB	0.3673	2809.95459	93.5870
2	12.336	BB	0.6071	192.54959	6.4130

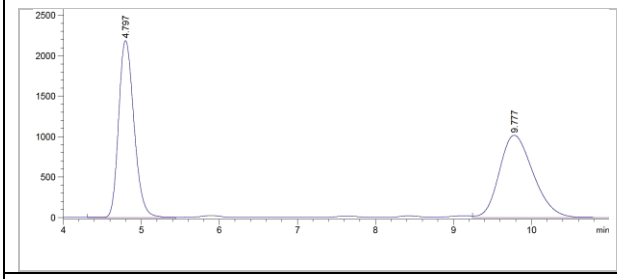


(*E*)-**18i** (*S*)-**22i**

Preparation of chiral secondary benzylic alcohol (*S*)-22i: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18i** (80 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22i** (64 mg, 74%) as a colorless oil: TLC analysis (1% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -39° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 7.5 Hz, h), 7.22-7.11 (3H, m, i+k), 4.97 (1H, dd, *J* = 6.5, 4.5 Hz, e), 4.12-3.98 (4H, m, b+b'), 3.37 (1H, br s, OH), 2.32 (3H, s, l), 2.04-1.79 (4H, m, c+d), 1.30 (3H, t, *J* = 7.0 Hz, a or a'), 1.29 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.38 (f), 134.36 (g), 130.47 (aryl), 127.30 (aryl), 126.33 (aryl), 125.38 (h), 70.03 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 61.79 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.73 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 30.67 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 22.09 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 19.14 (l), 16.56 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.95 ppm; IR (neat)

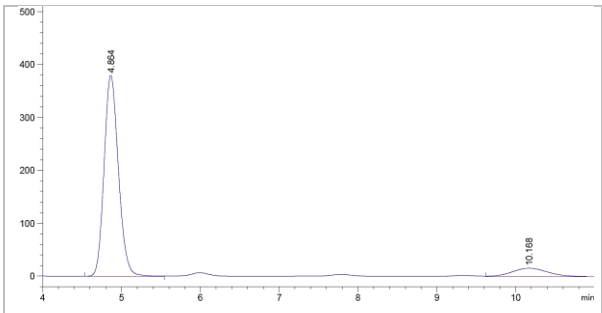
3361 (O-H), 2980 (aromatic C-H), 2930 (aliphatic C-H), 1485 (aromatic C=C), 1441 (aromatic C=C), 1391 (aromatic C=C), 1224 (P=O), 1020 (C-O), 957 (P-O), 755 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_4P+Na^+$ = 309.1232, found 309.1234 *m/z*; Enantiomer ratio = 91:9, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 ºC. HPLC traces:

(a) Racemate:

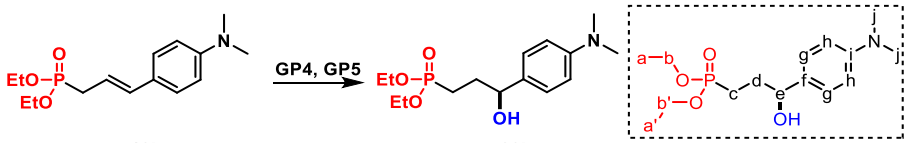


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.797	VV	0.2126	2.99077e4	49.4560
2	9.777	VBA	0.4678	3.05656e4	50.5440

(b) R:S = 9:91, CAHB of (*E*)-**18i** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22i**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.864	BB	0.1948	4785.50879	90.8853
2	10.168	VB	0.4807	479.92606	9.1147

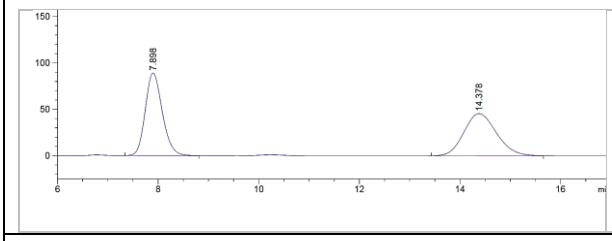


(*E*)-**18j** (*S*)-**22j**

Preparation of chiral secondary benzylic alcohol (*S*)-22j: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**; Note: 2 eq. of pinBH was used and CAHB carried out for 12 hours), the substrate (*E*)-**18j** (74.0 mg, 0.25 mmol)

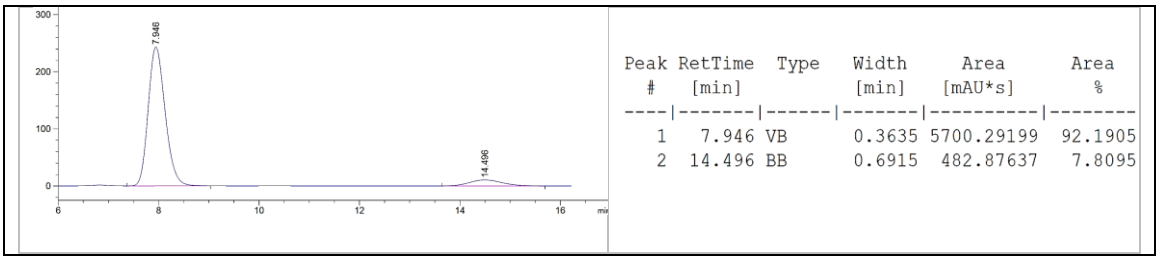
affords the chiral secondary benzylic alcohol (*S*)-**22j** (53 mg, 67%) as a colorless oil: TLC analysis (5% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -22° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (2H, d, *J* = 8.75 Hz, g), 6.70 (2H, d, *J* = 8.75 Hz, g), 4.61 (1H, dd, *J* = 7.0, 5.5 Hz, e), 4.14-3.98 (4H, m, b+b'), 2.93 (7H, s, j+OH), 2.08-1.66 (4H, m, c+d), 1.30 (3H, t, *J* = 7.0 Hz, a or a'), 1.29 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.35 (i), 131.98 (f), 126.94 (g), 112.71 (h), 73.77 (d, $^3J_{C\text{-}P}$ = 17 Hz, e), 61.67 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.65 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 40.81 (j), 31.62 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 22.20 (d, $^1J_{C\text{-}P}$ = 141 Hz, c), 16.57 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.94 ppm; IR (neat) 3351 (O-H), 2980 (aromatic C-H), 2904 (aliphatic C-H), 1617, 1522, 1225 (P=O), 1054 (C-O/C-N), 1022 (C-O/C-N), 945 (P-O), 815, 728 cm^{-1}; Note: *HRMS analysis was not successful on alcohol **9i** in detecting the molecular ion. The structure proof of **9i** is based on the NMR and IR analysis only.* Enantiomer ratio = 92:8, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate

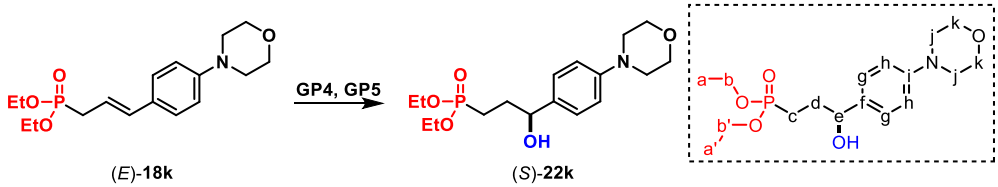


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	7.898	BB	0.3643	2101.46460	50.6734
2	14.378	BB	0.6987	2045.61108	49.3266

(b) R:S = 8:92, CAHB of (*E*)-**18j** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22j**



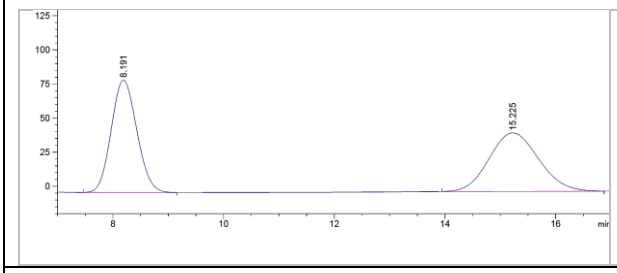
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	7.946	VB	0.3635	5700.29199	92.1905
2	14.496	BB	0.6915	482.87637	7.8095



Preparation of chiral secondary benzylic alcohol (*S*)-22k: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**; Note: 2 eq. of pinBH was used and CAHB carried out for 12 hours), the substrate (*E*)-**18k** (68 mg, 0.2 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22k** (39 mg, 55%) as a colorless oil: TLC analysis (10% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -20° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, d, *J* = 8.5 Hz, g), 6.91 (2H, d, *J* = 8.5 Hz, h), 4.71 (1H, t, *J* = 6.0 Hz, e), 4.17-4.04 (4H, m, b+b'), 3.88 (4H, t, *J* = 5.0 Hz, k), 3.17 (4H, t, *J* = 5.0 Hz, j), 2.09-1.96 (2H, m, d), 1.94-1.72 (2H, m, c), 1.33 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.08 (i), 135.36 (i), 127.00 (g), 115.85 (h), 73.82 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 67.10 (k), 61.86 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.83 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 49.55 (j), 31.79 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 22.28 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.68 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.82 ppm; IR (neat) 3355 (O-H), 2995 (aromatic C-H), 2901 (aliphatic C-H), 1525, 1226 (P=O), 1051 (C-O/C-N), 1022 (C-O/C-N), 949 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{28}NO_5P+Na^+$ = 380.1603, found 380.1603 *m/z*. Enantiomer ratio = 94:6, determined by chiral HPLC analysis: Stationary phase =

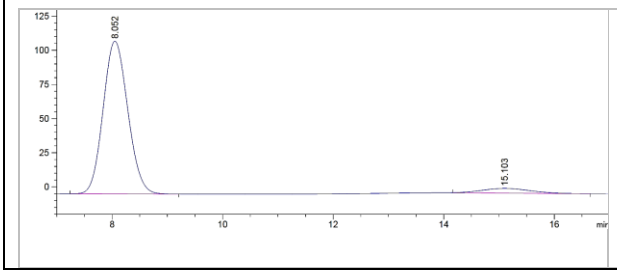
CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1.5 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate

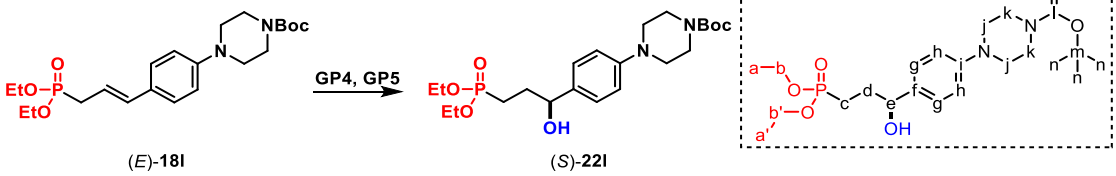


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.191	BB	0.5033	2649.93677	49.7782
2	15.225	BB	0.9745	2673.55615	50.2218

(b) R:S = 6:94, CAHB of (*E*)-**18k** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22k**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.052	VB	0.4848	3467.79956	94.4317
2	15.103	BB	0.7068	204.48552	5.5683

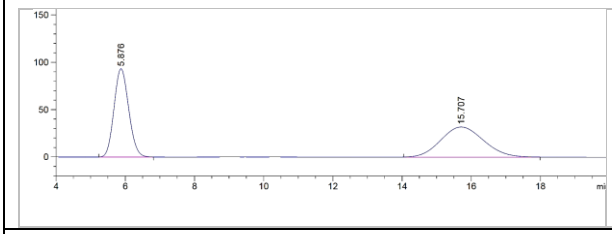


(*E*)-**18l** (*S*)-**22l**

Preparation of chiral secondary benzylic alcohol (*S*)-22l: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**; Note: 2 eq. of pinBH was used and CAHB carried out for 12 hours), the substrate (*E*)-**18l** (66.0 mg, 0.15 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22l** (47 mg, 68%) as a colorless oil: TLC analysis (6% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -20° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, *J* = 8.5 Hz, g), 6.90 (2H, d, *J* = 8.5 Hz, h), 4.67 (1H, t, *J* = 6.0 Hz, e), 4.14-4.00 (4H, m, b+b'), 3.57 (4H, t, *J* = 5.0 Hz, k), 3.12 (4H, t, *J* = 5.0 Hz,

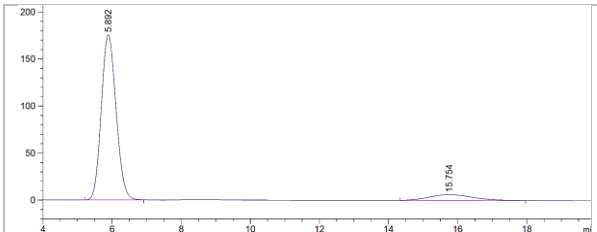
j), 2.09-1.94 (2H, m, d), 1.92-1.64 (2H, m, c), 1.49 (9H, s, n), 1.30 (6H, t, J = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.89 (l), 150.92 (i), 135.75 (f), 126.96 (g), 116.69 (h), 80.09 (m), 73.60 (d, $^{3}J_{C\text{-}P}$ = 16 Hz, e), 61.80 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.77 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 49.59 (j), 44.00 (k), 31.77 (d, $^{2}J_{C\text{-}P}$ = 4.5 Hz, d), 28.59 (n), 22.17 (d, $^{1}J_{C\text{-}P}$ = 141 Hz, c), 16.62 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.86 ppm; IR (neat) 3374 (O-H), 2977 (aromatic C-H), 2818 (aliphatic C-H), 1692 (C=O), 1421 (aromatic C=C), 1227 (P=O), 1022 (C-N/C-O), 959 (P-O), 751 cm^{-1}; HRMS (ESI) calculated for $C_{22}H_{37}N_2O_6P$+Na^+ = 479.2287, found 479.2287 *m/z*. Enantiomer ratio = 91:9, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1.5 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate

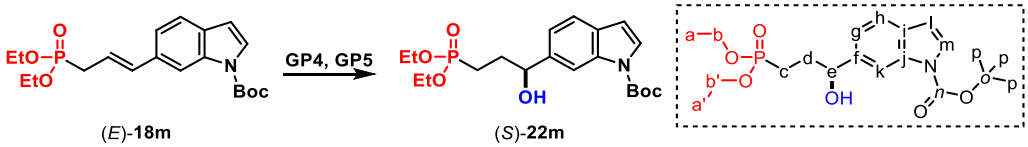


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.876	BB	0.4607	2747.60693	49.9971
2	15.707	BB	1.2837	2747.92358	50.0029

(b) R:S = 9:91, CAHB of (*E*)-**18l** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22l**



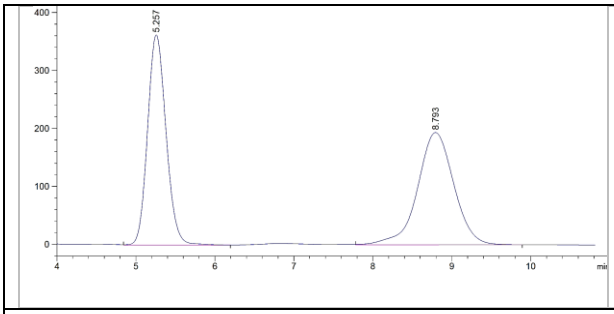
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.892	BB	0.4636	5203.43408	90.7742
2	15.754	BB	1.0301	528.84760	9.2258



(*E*)-**18m** (*S*)-**22m**

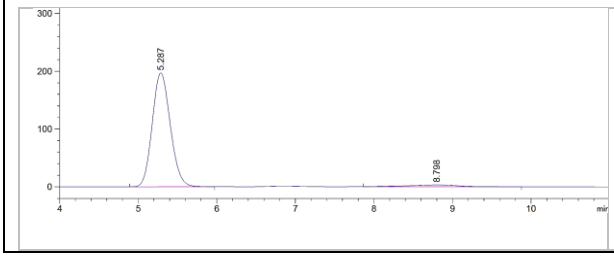
Preparation of chiral secondary benzylic alcohol (*S*)-22m: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**; Note: 2 eq. of pinBH was used in CAHB), the substrate (*E*)-**18m** (79 mg, 0.2 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22m** (64 mg, 78%) as a colorless oil: TLC analysis (2% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -42° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, br s, k), 7.58 (1H, d, *J* = 3.6 Hz, h), 7.53 (1H, d, *J* = 8.0 Hz, m), 7.25 (1H, dd, *J* = 8.0, 1.0 Hz, l), 6.55 (1H, d, *J* = 3.6 Hz, g), 4.87 (1H, t, *J* = 6.0 Hz, e), 4.13-4.00 (4H, m, b+b'), 2.97 (1H, br s, OH), 2.15-2.05 (2H, m, d), 1.97-1.73 (2H, m, c), 1.68 (9H, s, p), 1.31 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.86 (n),140.48 (j), 135.49 (f), 130.25 (i), 126.35 (h), 121.13 (m), 120.82 (l), 112.95 (k), 107.24 (g), 83.87 (o), 74.67 (d, $^3J_{C\text{-}P}$ = 16 Hz, e), 61.82 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.77 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 32.21 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 28.37 (p), 22.25 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.61 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.85 ppm; IR (neat) 3359 (O-H), 2981 (aromatic C-H), 2930 (aliphatic C-H), 1731 (C=O), 1438 (aromatic C=C), 1341 (aromatic C=C), 1251 (P=O), 1022 (C-O/C-N), 961 (P-O), 726 cm^{-1}; HRMS (ESI) calculated for $C_{20}H_{30}NO_6P+Na^+$ = 434.1708, found 434.1711 *m/z*; Enantiomer ratio = 96:4, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate:

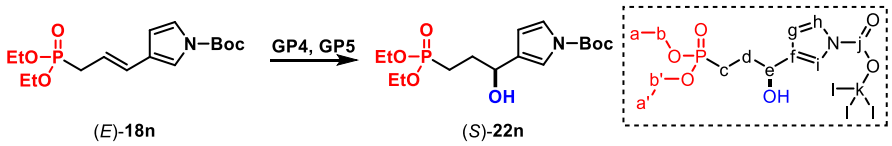


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.257	VB	0.2515	5891.37354	48.7316
2	8.793	BB	0.4900	6198.06885	51.2684

(b) R:S = 4:96, CAHB of (*E*)-**18m** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22m**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.287	BB	0.2484	3145.65259	95.8034
2	8.798	BB	0.5958	137.79367	4.1966

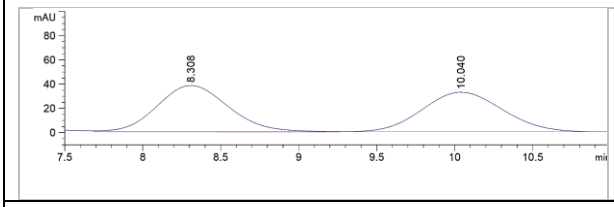


(*E*)-**18n** (*S*)-**22n**

Preparation of chiral secondary benzylic alcohol (*S*)-22n: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**; Note: 2 eq. of pinBH was used and CAHB carried out for 12 hours), the substrate (*E*)-**18n** (69 mg, 0.2 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22n** (62 mg, 86%) as a colorless oil: TLC analysis (3% methanol in ethyl acetate) $R_f = 0.5$; $[\alpha]_D^{20} = -23^o$ (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.18-7.17 (2H, m, h+i), 6.19 (1H, dd, *J* = 3.0, 2.0 Hz, g), 4.68 (1H, t, *J* = 6.0 Hz, e), 4.14-4.01 (4H, m, b+b'), 3.02 (1H, br s, OH), 2.08-1.74 (4H, m, c+d), 1.58 (9H, s, l), 1.31 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (162 MHz, $CDCl_3$) δ 148.96 (j), 130.57 (f), 120.77 (h or i), 116.83 (h or i), 110.25 (g), 83.85 (k), 68.11 (d, $^3J_{C\text{-}P}$ = 16 Hz, e), 61.81 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.78 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 30.89 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 28.13

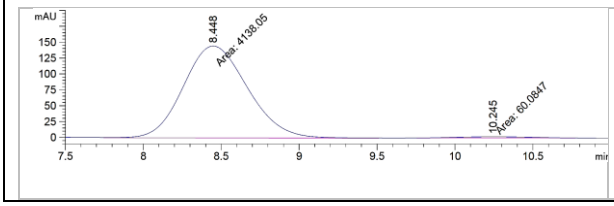
(l), 21.97 (d, $^{1}J_{C\text{-}P}$ = 142 Hz, c), 16.59 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.92 ppm; IR (neat) 3361 (O-H), 2980 (aromatic C-H), 2932 (aliphatic C-H), 1738 (C=O), 1485 (aromatic C=C), 1395 (aromatic C=C), 1346 (aromatic C=C), 1237 (P=O), 1155 (C-N), 1056 (C-O), 1023 (C-O), 967 (P-O), 729 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{28}NO_6P+Na^+$ = 384.1552, found 384.1553 *m/z*; Enantiomer ratio = 99:1, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 60:40 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 ^{o}C. HPLC traces:

(a) Racemate:

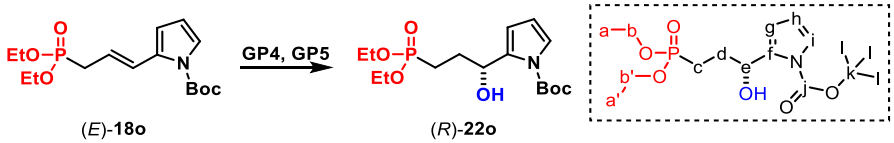


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.308	VB	0.4999	1220.43323	50.7821
2	10.040	BB	0.5680	1182.84241	49.2179

(b) R:S = 1:99, CAHB of (*E*)-**18n** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22n**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.448	MM	0.4770	4138.04736	98.5688
2	10.245	MM	0.5194	60.08473	1.4312

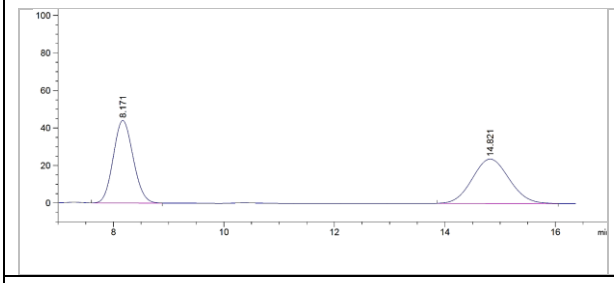


(*E*)-**18o** (*R*)-**22o**

Preparation of chiral secondary benzylic alcohol (*R*)-22o: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**; Note: 2 eq. of pinBH was used in CAHB), the substrate (*E*)-**18o** (69 mg, 0.2 mmol) affords the chiral secondary benzylic alcohol (*R*)-**22o** (61 mg, 85%) as a colorless oil: TLC analysis (2% methanol in

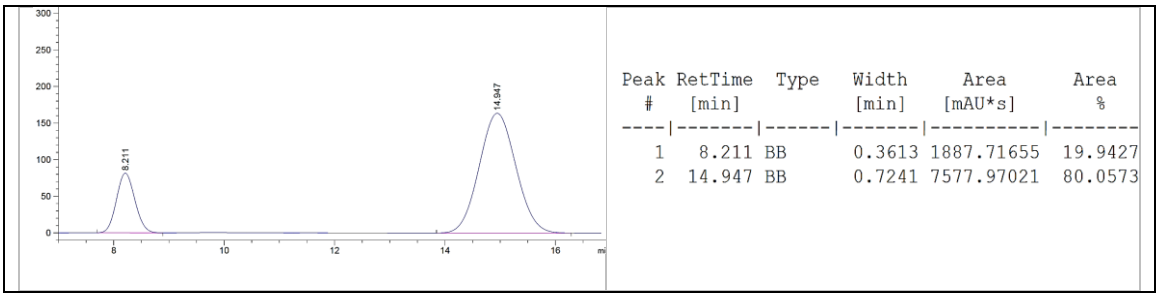
ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -0.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.14 (1H, m, i), 6.20-6.19 (1H, m, h), 6.08 (1H, t, *J* = 3.5 Hz, g), 4.87 (1H, t, *J* = 6.5 Hz, e), 4.26-4.02 (5H, m, b+b'+OH), 2.20-2.02 (3H, m, c(1H)+d), 1.89-1.74 (1H, m, c(1H)), 1.59 (9H, s, l), 1.31 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.36 (j), 137.38 (f), 122.16 (i), 111.77 (h), 110.49 (g), 84.78 (k), 66.62 (d, $^3J_{C-P}$ = 18 Hz, e), 61.65 (d, $^2J_{C-P}$ = 6.0 Hz, b or b'), 61.63 (d, $^2J_{C-P}$ = 6.0 Hz, b or b'), 28.09 (l), 27.77 (d, $^2J_{C-P}$ = 4.25 Hz, d), 22.58 (d, $^1J_{C-P}$ = 142 Hz, c), 16.56 (d, $^3J_{C-P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.56 ppm; IR (neat) 3372 (O-H), 2980 (aliphatic C-H), 2933 (aromatic C-H), 1735 (C=O), 1325, 1228 (P=O), 1054 (C-O), 1022 (C-O), 960 (P-O), 722 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{28}NO_6P$+Na^+ = 384.1552, found 384.1555 *m/z*; Enantiomer ratio = 80:20, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 60:40 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate

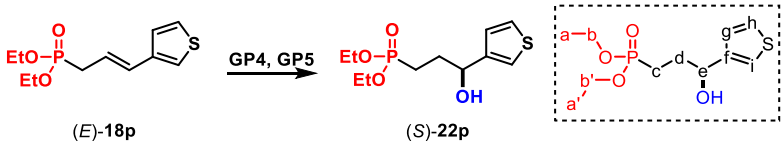


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.171	VB	0.3908	1100.58521	50.0800
2	14.821	BB	0.7195	1097.07043	49.9200

(b) R:S = 80:20, CAHB of (*E*)-**18o** using (*R*)-**B2** followed by oxidation to yield (*R*)-**22o**:



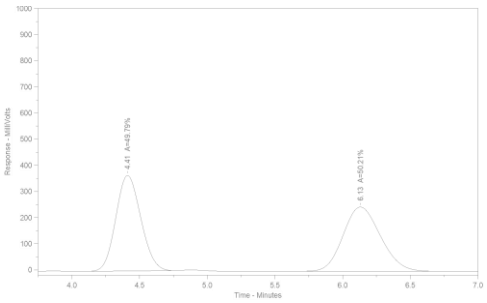
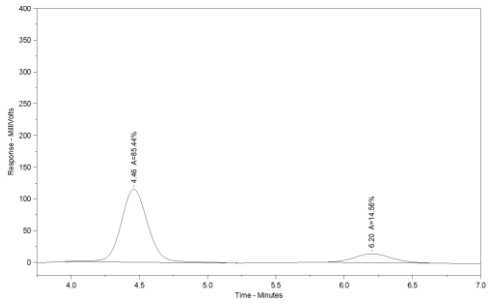
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.211	BB	0.3613	1887.71655	19.9427
2	14.947	BB	0.7241	7577.97021	80.0573

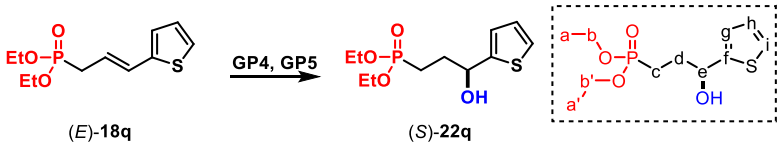


(*E*)-**18p** (*S*)-**22p**

Preparation of chiral secondary benzylic alcohol (*S*)-9o: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18p** (78 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22p** (69 mg, 83%) as a colorless oil: TLC analysis (2% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -20° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, dd, *J* = 5.0, 3.0 Hz, h), 7.24-7.23 (1H, m, i), 7.08 (1H, dd, *J* = 5.0, 1.25 Hz, g), 4.91-4.87 (1H, m, e), 4.17-4.03 (4H, m, b+b'), 3.02 (1H, d, *J* = 4.0 Hz, OH), 2.17-2.02 (2H, m, d), 1.95-1.79 (2H, m, c), 1.34 (3H, t, *J* = 7.0 Hz, a or a'), 1.33 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.56 (f), 126.45 (h), 125.71 (g), 121.09 (i), 70.34 (d, $^3J_{C\text{-}P}$ = 15 Hz, e), 61.93 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.90 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 31.37 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 22.01 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.66 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.85 ppm; IR (neat) 3368 (O-H), 2983 (aromatic C-H), 2905 (aliphatic C-H), 1441 (aromatic C=C), 1391 (aromatic C=C), 1224 (P=O), 1052 (C-O), 1020 (C-O), 956 (P-O), 784 cm^{-1}; HRMS (ESI) calculated for $C_{11}H_{19}O_4PS+Na^+$ = 301.0639, found 301.0641 *m/z*; Enantiomer ratio = 85:15, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile

Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1.5 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate:	(b) R:S = 15:85, CAHB of (*E*)-**18p** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22p**:
	

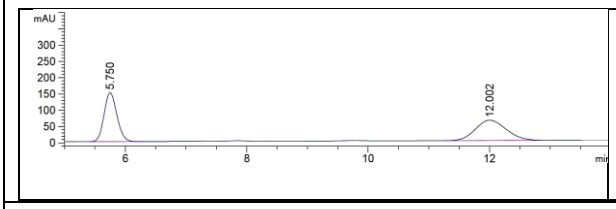


(*E*)-**18q** (*S*)-**22q**

Preparation of chiral secondary benzylic alcohol (*S*)-22q: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18q** (78 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22q** (67 mg, 80%) as a colorless oil: TLC analysis (2% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -13° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (1H, dd, *J* = 4.5, 2.0 Hz, i), 6.95-6.93 (2H, m, g+h), 4.97 (1H, t, *J* = 6.0 Hz, e), 4.11-3.97 (4H, m, b+b'), 2.13-2.04 (2H, m, d), 1.99-1.69 (2H, m, c), 1.29 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.40 (f), 126.75 (h), 124.44 (i), 123.61 (g), 69.69 (d, $^3J_{C\text{-}P}$ = 16 Hz, e), 61.87 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.82 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 32.22 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 21.88 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.54 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.58 ppm; IR (neat)

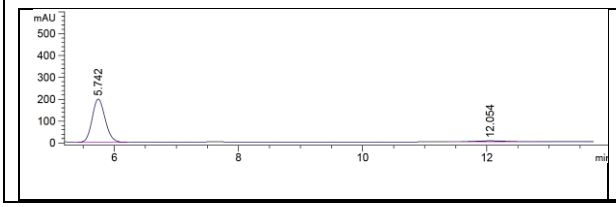
3360 (O-H), 2980 (aromatic C-H), 2904 (aliphatic C-H), 1440 (aromatic C=C), 1391 (aromatic C=C), 1219 (P=O), 1017 (C-O), 958 (P-O), 697 cm^{-1}; HRMS (ESI) calculated for $C_{11}H_{19}O_4PS+Na^+$ = 301.0639, found 301.0639 *m/z*; Enantiomer ratio = 95:5, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 40:60 Isopropanol:Hexanes; Flow rate = 1.5 mL/min; HPLC UV Detector λ = 210 nm, 25 ºC. HPLC traces:

(a) Racemate

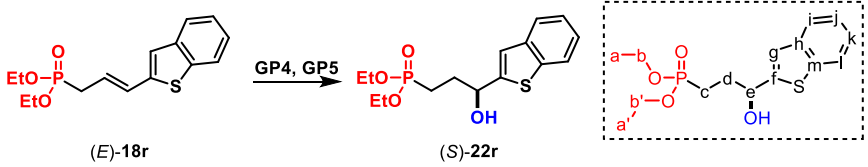


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.750	VB	0.2283	2203.71069	49.8917
2	12.002	BB	0.5534	2213.28174	50.1083

(b) R:S = 5:95, CAHB of (*E*)-**18q** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22q**.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.742	VB	0.2264	2871.94727	95.0985
2	12.054	BB	0.5312	148.02408	4.9015

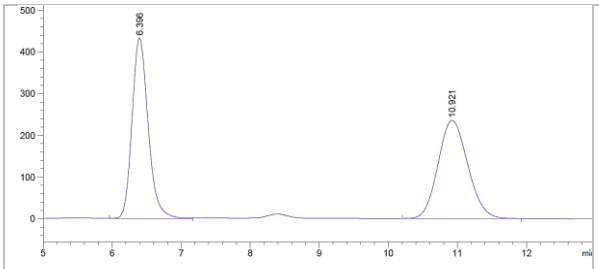


(*E*)-**18r** (*S*)-**22r**

Preparation of chiral secondary benzylic alcohol (*S*)-22r: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18r** (77.6 mg, 0.25 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22r** (53 mg, 65%) as a waxy solid: TLC analysis (1% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -21º (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.79 (2H, m, i or l), 7.71-7.69 (2H, m, i or l),

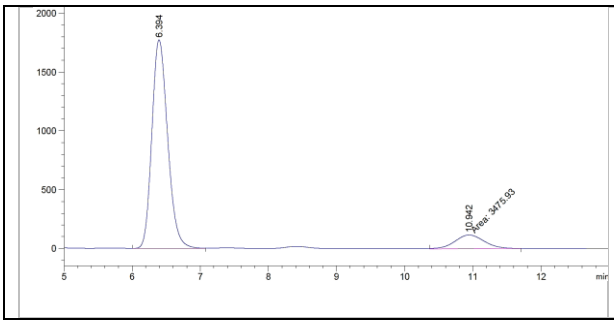
7.36-7.27 (2H, m, j+k), 7.19 (1H, s, g), 5.07 (1H, t, J = 6.0 Hz, e), 4.23-3.99 (5H, m, b+b'+OH), 2.22-2.13 (2H, m, d), 1.98-1.80 (2H, m, c), 1.30 (3H, t, J = 7.0 Hz, a or a'), 1.29 (3H, t, J = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.07 (f), 139.75 (h), 139.46 (m), 124.38 (j or k), 124.20 (j or k), 123.56 (i or l), 122.56 (i or l), 120.21 (g), 70.17 (d, $^{3}J_{C\text{-}P}$ = 15 Hz, e), 62.00 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.93 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 31.91 (d, $^{2}J_{C\text{-}P}$ = 4.5 Hz, d), 21.77 (d, $^{1}J_{C\text{-}P}$ = 142 Hz, c), 16.56 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.54 ppm; IR (neat) 3252 (O-H), 2979 (aromatic C-H), 2927 (aliphatic C-H), 1219 (P=O), 1027 (C-O), 1011 (C-O), 950 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{21}O_4PS+Na^+$ = 351.0796, found 351.0798 *m/z*; Enantiomer ratio = 89:11, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 40:60 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate:

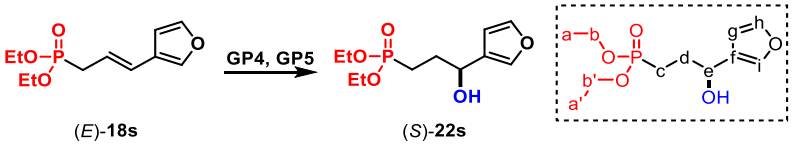


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	6.396	VB	0.2505	7018.30811	49.9438
2	10.921	BB	0.4663	7034.09570	50.0562

(b) R:S = 11:89, CAHB of (*E*)-**18r** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22r**:



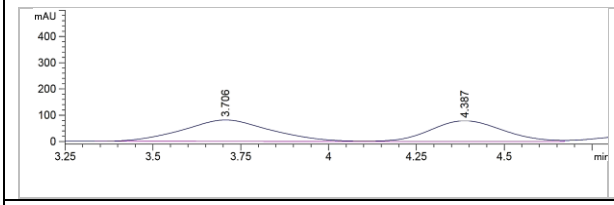
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	6.394	VV	0.2496	2.85179e4	89.1356
2	10.942	MM T	0.4977	3475.92603	10.8644



Preparation of chiral secondary benzylic alcohol (*S*)-22s: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18s** (73 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22s** (60 mg, 76%) as a colorless oil: TLC analysis (3% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -5.5° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.35 (2H, m, h+i), 6.37 (1H, br s, g), 4.70 (1H, t, *J* = 6.0 Hz, e), 4.12-3.98 (4H, m, b+b'), 3.64 (1H, br s, OH), 2.05-1.72 (4H, m, c+d), 1.29 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.41 (h), 139.27 (i), 128.69 (f), 108.60 (g), 66.55 (d, $^3J_{C\text{-}P}$ = 16 Hz, e), 61.84 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.81 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 30.76 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 21.79 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.55 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.85 ppm; IR (neat) 3357 (O-H), 2982 (C-H), 1501 (aromatic C=C), 1442 (aromatic C=C), 1391 (aromatic C=C), 1222 (P=O), 1159, 1016 (C-O), 957 (P-O), 873, 788, 600 cm^{-1}; HRMS (ESI) calculated for $C_{11}H_{19}O_5P+Na^+$ = 285.0862, found 285.0867 *m/z*; Enantiomer ratio = 83:17, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 60:40

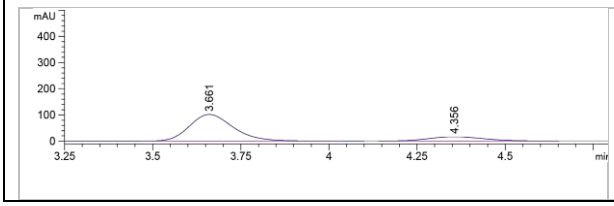
Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate

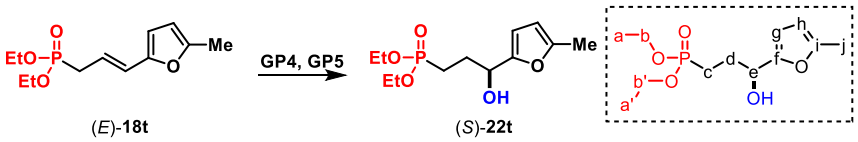


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	3.706	BV	0.2524	1417.37683	55.7812
2	4.387	VV	0.2222	1123.58179	44.2188

(b) R:S = 17:83, CAHB of (*E*)-**18s** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22s**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	3.661	BB	0.1328	876.91345	83.1618
2	4.356	BV	0.1665	177.55312	16.8382

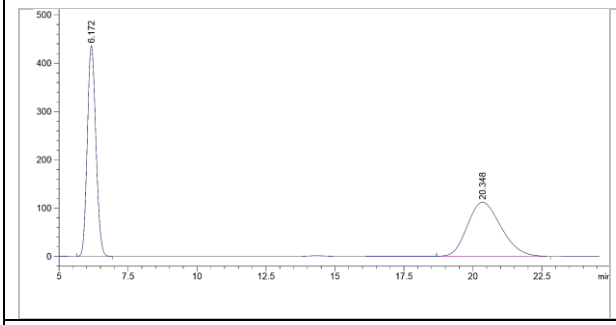


(*E*)-**18t** (*S*)-**22t**

Preparation of chiral secondary benzylic alcohol (*S*)-22t: Following the general procedure for sequential hydroboration-oxidation (**GP4**/**GP5**), the substrate (*E*)-**18t** (77 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22t** (68 mg, 82%) as a colorless oil: TLC analysis (3% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -11° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (1H, d, *J* = 3.0 Hz, g), 5.87 (1H, dd, *J* = 3.0, 1.0 Hz, h), 4.65 (1H, t, *J* = 6.5 Hz, e), 4.13-3.99 (4H, m, b+b'), 3.44 (1H, br s, OH), 3.16 (3H, s, j), 2.15-2.00 (2H, m, d), 1.93-1.72 (2H, m, c), 1.29 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.36 (f), 151.73 (i), 107.01 (g), 106.12 (h), 67.44 (d, $^3J_{C\text{-}P}$ = 17 Hz, e), 61.82 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.80 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 28.62 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 21.88 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.54 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a'), 13.64 (j)

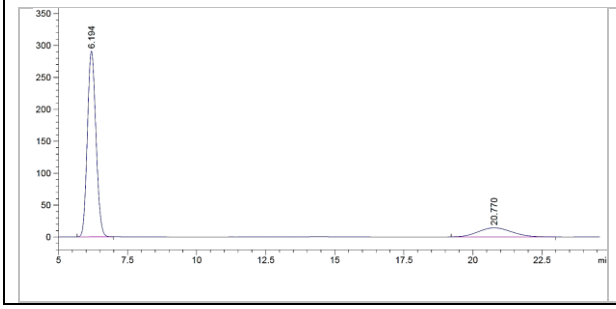
ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.63 ppm; IR (neat) 3353 (O-H), 2982 (aromatic C-H), 2925 (aliphatic C-H), 1566, 1442 (aromatic C=C), 1391 (aromatic C=C), 1220 (P=O), 1018 (C-O), 956 (P-O), 784 cm^{-1}; HRMS (ESI) calculated for $C_{12}H_{21}O_5P+Na^+$ = 299.1024, found 299.1023 *m/z*; Enantiomer ratio = 84:16, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1.5 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate

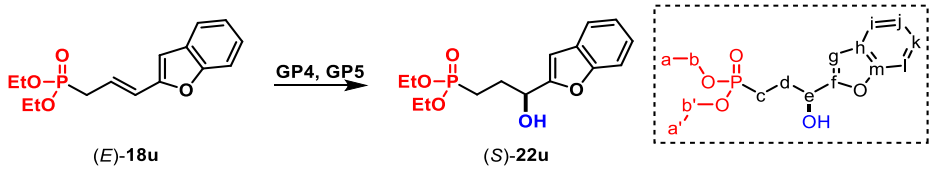


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	6.172	BB	0.3386	9442.63574	49.9660
2	20.348	BB	0.2935	9455.47266	50.0340

(b) R:S = 16:84, CAHB of (*E*)-**18t** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22t**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	6.194	BB	0.3380	6284.61719	83.9406
2	20.770	BB	1.2673	1202.36584	16.0594

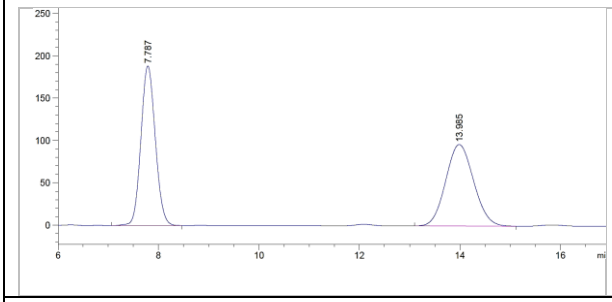


(*E*)-**18u** (*S*)-**22u**

Preparation of chiral secondary benzylic alcohol (*S*)-22u: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18u** (73.6

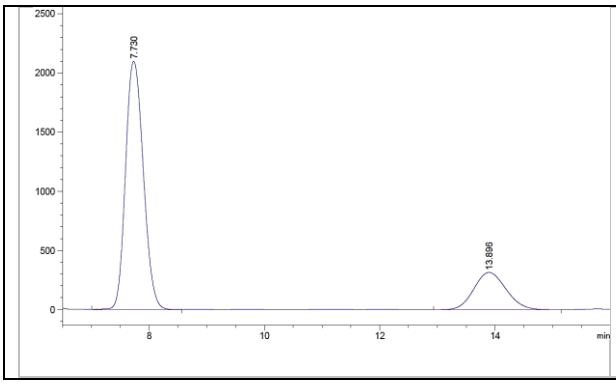
mg, 0.25 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22u** (43 mg, 55%) as a light yellow oil: TLC analysis (2% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -18° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (2H, m, i), 7.45-7.43 (2H, m, l), 7.28-7.19 (2H, m, j+k), 6.67 (1H, s, g), 4.90 (1H, dd, *J* = 7.0, 5.5 Hz, d), 4.13-4.02 (5H, m, b+b'+OH), 2.32-2.13 (2H, m, d), 1.99-1.81 (2H, m, c), 1.31 (3H, t, *J* = 7.0 Hz, a or a'), 1.29 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.13 (f), 154.92 (m), 128.32 (h), 124.16 (j or k), 122.89 (j or k), 121.15 (i), 111.32 (l), 102.98 (g), 67.78 (d, $^3J_{C-P}$ = 15 Hz, e), 62.03 (d, $^2J_{C-P}$ = 6.0 Hz, b or b'), 61.01 (d, $^2J_{C-P}$ = 6.0 Hz, b or b'), 28.71 (d, $^2J_{C-P}$ = 4.5 Hz, d), 21.56 (d, $^1J_{C-P}$ = 142 Hz, c), 16.55 (d, $^3J_{C-P}$ = 5.5 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.71 ppm; IR (neat) 3309 (O-H), 2981 (aromatic C-H), 2907 (aliphatic C-H), 1454 (aromatic C=C), 1224 (P=O), 1021 (C-O), 956 (P-O), 804 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{21}O_5P+Na^+$ = 335.1024, found 335.1031 *m/z*; Enantiomer ratio = 89:11, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 40:60 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate

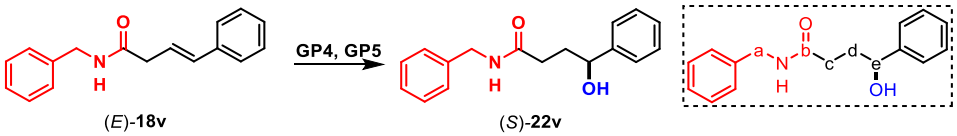


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	7.787	VB	0.3106	3764.61792	50.2179
2	13.985	BB	0.6036	3731.95068	49.7821

(b) R:S = 21:79, CAHB of (*E*)-**18u** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22u**:



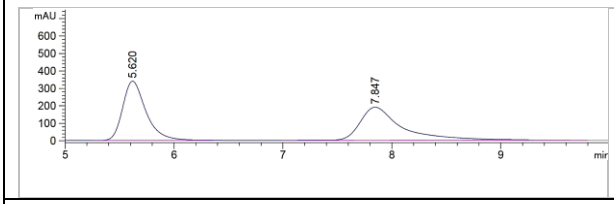
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	7.730	BB	0.3389	4.51091e4	78.7184
2	13.896	BB	0.6064	1.21953e4	21.2816



(*E*)-**18v** (*S*)-**22v**

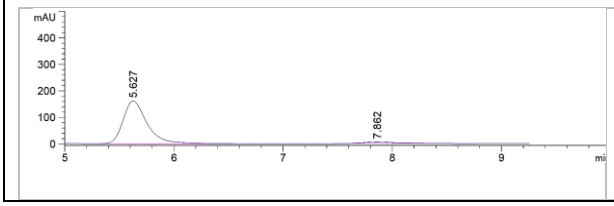
Preparation of chiral secondary benzylic alcohol (*S*)-22v: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18v** (75 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22v** (63 mg, 78%) as a white solid (regioisomeric ratio, rr = 7:1): Melting point = 124-125 ^{o}C; TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -50^{o} (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (10 H, m, aryl), 6.39 (1H, br s, NH), 4.72 (1H, br s, e), 4.37 (2H, d, *J* = 5.75 Hz, a), 4.15 (1H, br s, OH), 2.35-2.31 (2H, m, c), 2.11-1.96 (1H, m, d) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.69 (b), 144.58 (aryl), 138.27 (aryl), 128.82 (aryl), 128.51 (aryl), 127.89 (aryl), 127.63 (aryl), 127.46 (aryl), 125.88 (aryl), 73.57 (e), 43.80 (a), 34.58 (d), 32.96 (c) ppm; IR (neat) 3297 (O-H), 3009 (C-H), 1639 (C=O), 1544, 1494 (aromatic C=C), 1453 (aromatic C=C), 1216, 1060 (C-O), 1027 (C-O), 746, 697, 666 cm^{-1}; Enantiomer ratio = 94:6, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 25:75 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 ^{o}C. HPLC traces:

(a) Racemate



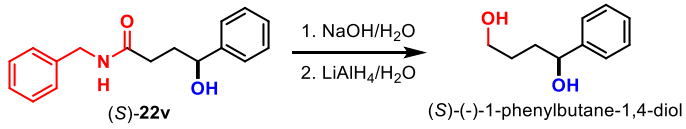
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.620	VB	0.2240	5026.27832	49.9635
2	7.847	BB	0.3842	5033.62109	50.0365

(b) R:S = 6:94, CAHB of (*E*)-**18v** using (*R*)-**B1** followed by oxidation to yield (*S*)-**22v**:

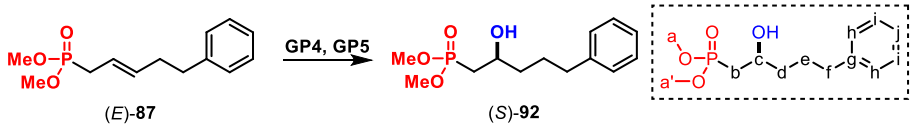


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.627	BB	0.2294	2449.29272	94.0400
2	7.862	BB	0.3625	155.23045	5.9600

Absolute Configuration Assignment: The amide-functionalized chiral secondary benzyl alcohol **22v** obtained from (*E*)-**18v** via CAHB using (*R*)-**B2** followed by oxidation was converted to 1-phenylbutane-1,4-diol ($[\alpha]_D^{20}$ = -45° (*c* = 1.0, $CHCl_3$)) via sequential hydrolysis ($NaOH/H_2O$) and reduction ($LiAlH_4$). 1-phenylbutane-1,4-diol is a previously reported compound in the literature[14] and the negative value of optical rotation is expected for the (*S*)-enantiomer. Hence, the chiral secondary benzyl alcohol **22v** is assigned *"S"*.



(*S*)-**22v** (*S*)-(-)-1-phenylbutane-1,4-diol

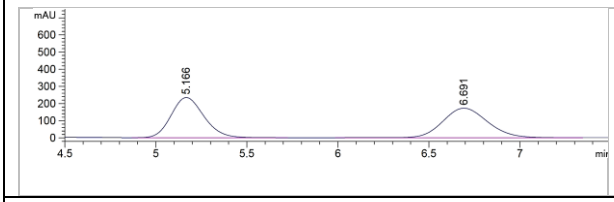


(*E*)-**87** (*S*)-**92**

Preparation of chiral secondary alcohol (*S*)-92: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**87** (76 mg, 0.3 mmol) affords the chiral secondary alcohol (*S*)-**92** (38 mg, 47%) as a colorless oil (**Note:** About a

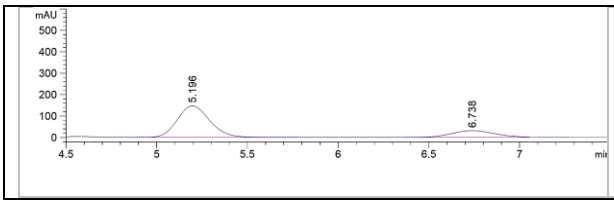
3:1:1 ratio of the β-regioisomer : γ-regioisomer : reduced product is formed in CAHB. Yield after oxidation is low because of the high polarity of the products and the potential hydrolysis of the methyl phosphonate. This example is carried for the absolute configuration assignment of the product (*S*)-**37** (*vide infra*)): TLC analysis (5% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +9.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.18 (5H, m, aryl), 4.05-4.03 (1H, m, c), 3.76 (3H, d, $^3J_{P\text{-}H}$ = 11 Hz, a or a'), 3.74 (3H, d, $^3J_{P\text{-}H}$ = 11 Hz, a or a'), 3.46 (1H, br s, OH), 2.65 (2H, t, *J* = 7.5 Hz, f), 2.01-1.49 (4H, m, d+e) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.32 (g), 128.57 (h or i), 128.47 (h or i), 125.94 (j), 66.48 (d, $^2J_{C\text{-}P}$ = 5.5 Hz, d), 52.62 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, a or a'), 52.59 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, a or a'), 37.92 (d, $^3J_{C\text{-}P}$ = 17 Hz, d), 35.80 (f), 32.72 (d, $^1J_{C\text{-}P}$ = 138 Hz, b), 27.36 (d, $^4J_{C\text{-}P}$ = 1.0 Hz, e) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.08 ppm; IR (neat) 3375 (O-H), 2950 (aromatic C-H), 2852 (aliphatic C-H), 1496 (aromatic C=C), 1453 (aromatic C=C), 1223 (P=O), 1023 (C-O), 842, 817, 749, 699 cm^{-1}; Enantiomer ratio = 77:23, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 60:40 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate



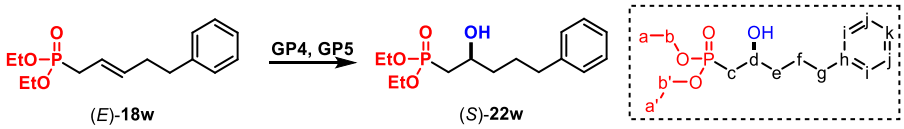
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.166	VB	0.1944	2938.63208	49.9252
2	6.691	BB	0.2658	2947.43970	50.0748

(b) R:S = 23:77, CAHB of (*E*)-**87** using (*R*)-**B2** followed by oxidation to yield (*S*)-**92**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.196	VB	0.1922	1834.83081	77.4636
2	6.738	BB	0.2643	533.80627	22.5364

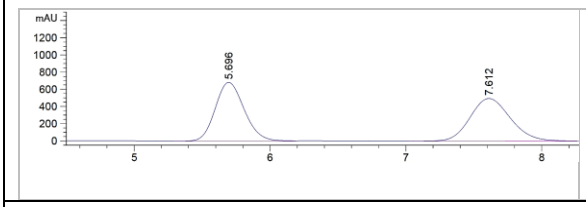
Absolute Configuration Assignment: The dimethyl phosphonate substrate (*E*)-**87** is prepared because the product alcohol **92** is a previously reported compound in the literature.[15] CAHB of (*E*)-**87** using (*R*)-**B2** followed by oxidation yields **92** with a positive value of optical rotation ($[\alpha]_D^{20}$ = +9.5° (*c* = 1.0, $CHCl_3$)) which is expected for the *"S"* enantiomer. The configuration of chiral secondary alkyl alcohol **22w** (*vide infra*) is based on analogy to this assignment.



Preparation of chiral secondary alcohol (*S*)-22w: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18w** (85 mg, 0.3 mmol) affords the chiral secondary alcohol (*S*)-**22w** (54 mg, 60%) as a colorless oil: TLC analysis (2% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +8.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.17 (5H, m, aryl), 4.20-4.02 (5H, m, b+d), 3.58 (1H, br s, OH), 2.65 (2H, t, *J* = 7.5 Hz, g), 2.00-1.49 (c+e+f), 1.34 (3H, t, *J* = 7.0 Hz, a or a'), 1.33 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.37 (h), 128.57 (i or j), 128.46 (i or j), 125.91 (k), 66.53 (d, $^2J_{C\text{-}P}$ = 5.5 Hz, d), 62.02 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 37.88 (d, $^3J_{C\text{-}P}$ = 17 Hz, e), 35.84 (g), 33.66 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 27.38 (f), 16.59 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.56 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.51 ppm; IR (neat) 3377 (O-H), 2981 (aromatic C-H), 2930 (aliphatic C-H), 1496 (aromatic C=C), 1453

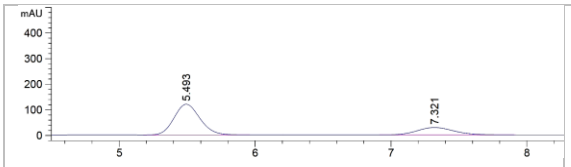
(aromatic C=C), 1391 (aromatic C=C), 1219 (P=O), 1020 (C-O), 957 (P-O), 698 cm^{-1}; Enantiomer ratio = 75:25, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate:



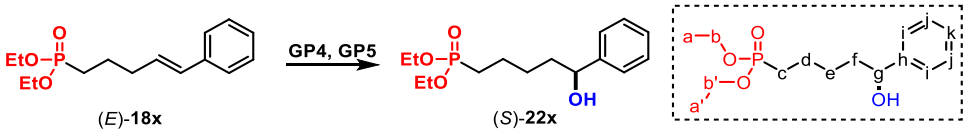
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.696	VV	0.2320	1.02209e4	49.92
2	7.612	VV	0.3210	1.02504e4	50.07

(b) R:S = 25:75, CAHB of (*E*)-**18w** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22w**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.493	VB	0.2041	1582.53699	74.50
2	7.321	VB	0.2924	541.52081	25.49

Absolute Configuration Assignment: The absolute configuration of alcohol **22w** is based on analogy to the assignment of alcohol **92**.

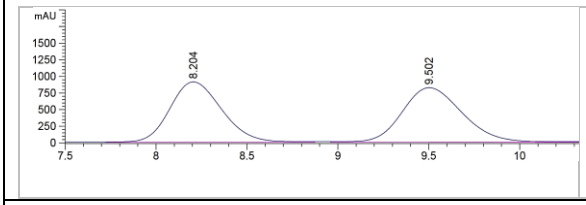


(*E*)-**18x** (*S*)-**22x**

Preparation of chiral secondary alcohol (*S*)-22x: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**18x** (85 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**22x** (43 mg, 47%) as a colorless oil (**Note:** About a 2.5:1 ratio of benzylic : non-benzylic boronic esters is estimated from ^{31}P NMR of crude CAHB mixture): TLC analysis (3% methanol in ethyl acetate) $R_f = 0.5$; $[\alpha]_D^{20}$ = -

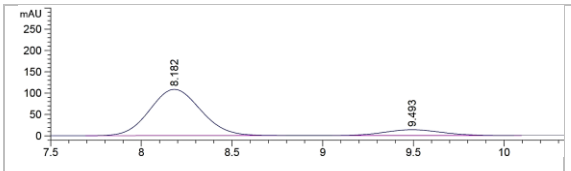
4.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.18 (5H, m, aryl), 4.63 (1H, t, *J* = 6.5 Hz, g), 4.08-3.97 (4H, m, b+b'), 2.99 (1H, br s, OH), 1.83-1.32 (8H, m, c+d+e+f), 1.27 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.20 (h), 128.44 (i or j), 127.44 (k), 125.99 (i or j), 74.06 (g), 61.53 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 38.70 (f), 26.90 (d or e), 26.73 (d or e), 25.62 (d, $^1J_{C\text{-}P}$ = 141 Hz, c), 16.55 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.31 ppm; IR (neat) 3370 (O-H), 2981 (aromatic C-H), 2932 (aliphatic C-H), 1452 (aromatic C=C), 1391 (aromatic C=C), 1218 (P=O), 1051 (C-O), 1020 (C-O), 956 (P-O), 700 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{25}O_4P+Na^+$ = 323.1388, found 323.1395 *m/z*; Enantiomer ratio = 88:12, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 75:25 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate



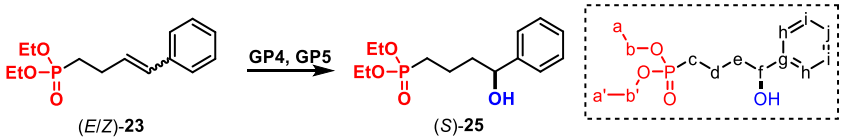
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.204	VB	0.3104	1.82104e4	48.91
2	9.502	BB	0.3593	1.90216e4	51.08

(b) R:S = 12:88, CAHB of (*E*)-**18x** using (*R*)-**B2** followed by oxidation to yield (*S*)-**22x**



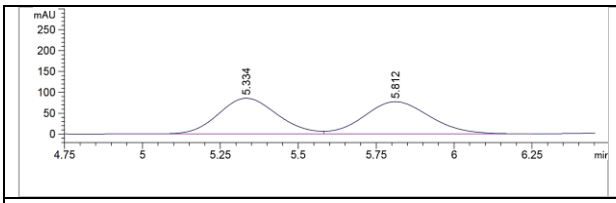
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.182	BB	0.3053	2122.38354	87.74
2	9.493	BB	0.3435	296.31558	12.25

Absolute Configuration Assignment: See section 5.11.6. Kinetic Acylation of Chiral Secondary Benzylic Alcohols using Benzotetramisole (BTM).



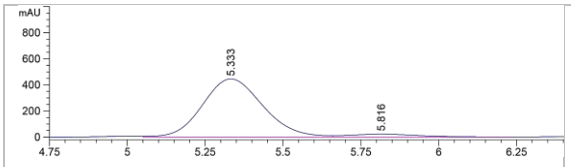
Preparation of chiral secondary alcohol (*S*)-25: Following the general procedure for sequential hydroboration-oxidation (**GP4/GP5**), the substrate (*E*)-**23** (80 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**25** (68 mg, 79%) as a colorless oil. Alternatively, the substrate (*Z*)-**23** (80 mg, 0.3 mmol) affords the chiral secondary benzylic alcohol (*S*)-**25** (70 mg, 81%) as a colorless oil: (**Note:** >20:1 regioisomeric ratio of benzylic : non-benzylic boronic esters is estimated from ^{31}P NMR of crude CAHB mixture): TLC analysis (3% methanol in ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -16^o (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.13 (5H, m, aryl), 4.61 (1H, dd, *J* = 7.0, 4.5 Hz, f), 4.05-3.92 (4H, m, b+b'), 3.49 (1H, br s, OH), 1.84-1.51 (6H, m, c+d+e), 1.25 (3H, t, *J* = 7.0 Hz, a or a'), 1.24 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.08 (g), 128.39 (h or i), 127.35 (j), 125.91 (h or i), 73.57 (f), 61.54 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 39.84 (d, $^3J_{C\text{-}P}$ = 16 Hz, e), 25.39 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 18.95 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 16.48 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.24 ppm; IR (neat) 3365 (O-H), 2979 (aromatic C-H), 2905 (aliphatic C-H), 1492 (aromatic C=C), 1452 (aromatic C=C), 1391 (aromatic C=C), 1226 (P=O), 1020 (C-O), 955 (P-O), 700 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_4P$+Na^+ = 309.1232, found 309.1239; Enantiomer ratio = 95:5, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 ^{o}C. HPLC traces:

(a) Racemate



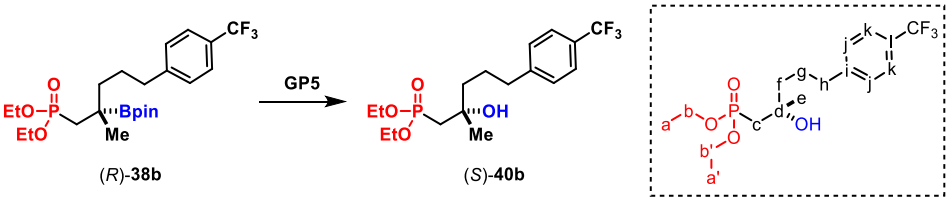
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.334	BV	0.2044	1125.28809	49.7661
2	5.812	VV	0.2276	1135.86536	50.2339

(b) R:S = 5:95, CAHB of (*E*/*Z*)-**23** using (*R*)-**B2** followed by oxidation to yield (*S*)-**25**:



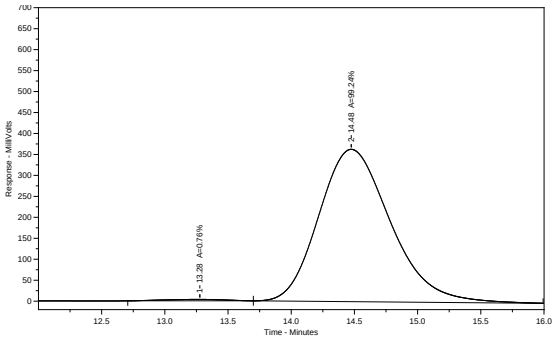
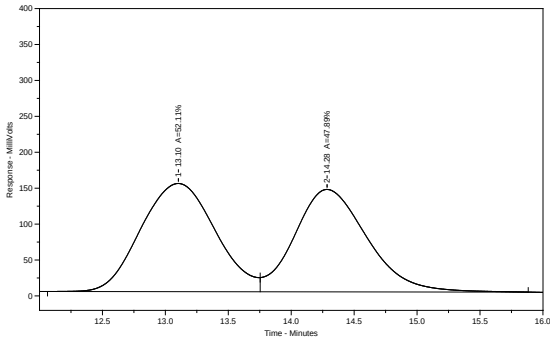
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.333	VV	0.2092	6003.92041	94.58
2	5.816	VV	0.2342	343.43286	5.41

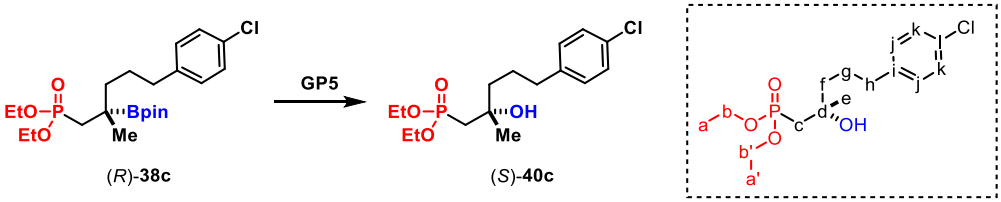
Absolute Configuration Assignment: See section 5.11.6. Kinetic Acylation of Chiral Secondary Benzylic Alcohols using Benzotetramisole (BTM).



Synthesis of chiral tertiary alcohol (*S*)-**40b:** Following the general procedure for oxidation of chiral tertiary boronic esters **GP5**, the chiral tertiary boronic ester (*R*)-**38b** (64 mg, 0.13 mmol) yields the chiral tertiary alcohol (*S*)-**40b** (47 mg, 95%) as a colorless viscous oil: TLC analysis (ethyl-acetate:hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = –5.8° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (2H, d, *J* = 8.0 Hz, k), 7.31 (2H, d, *J* = 8.0 Hz, k), 4.19-4.06 (4H, m, b+b'), 3.96 (1H, s, OH), 2.70 (2H, t, *J* = 7.4 Hz, h), 2.07-2.92 (2H, m, c), 1.79-1.61 (4H, m, f+g), 1.36-1.31 (9H, m, a+a'+e) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.53 (aryl), 128.81 (aryl), 125.39 (aryl), 125.36 (aryl), 125.32 (aryl), 125.28 (aryl), 70.46 (d, $^2J_{C\text{-}P}$ = 5 Hz, d), 61.77 (dd, $^2J_{C\text{-}P}$ = 7.0, 4.0 Hz, b+b'), 43.03 (d, $^3J_{C\text{-}P}$ = 11 Hz, f), 37.41 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 36.09 (h), 28.10 (d, $^3J_{C\text{-}P}$ = 10 Hz, e), 25.77 (g), 16.48 (d, $^3J_{C\text{-}}$

$_P$ = 5 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.96 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.31 ppm; IR (neat) 3398 (O-H), 2982 (Aromatic C-H), 2942 (Aliphatic C-H), 1618, 1640, 1416, 1391, 1323 (C-F), 1222 (P=O), 1161, 1117 (C-O), 1018 (C-O), 959 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{26}F_3NaO_4P+Na^+$ 405.1413, found 405.1420 *m/z*. Enantiomer ratio = >99:1, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 1:1 isopropanol:hexanes; Flow rate = 0.5 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

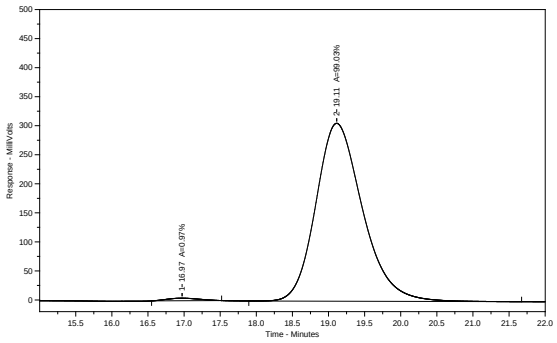
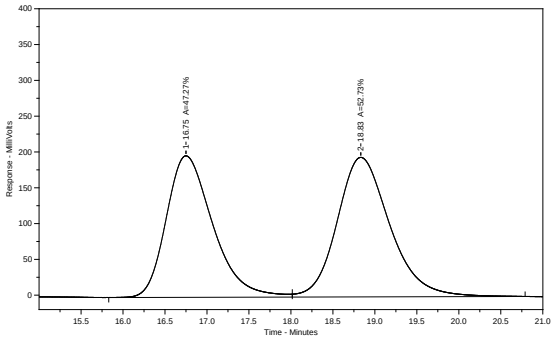
(a). R:S = 1:99, CAHB of **37b** with (*R*,*R*)-**T2**, then oxidation:	(b). Racemate:
	

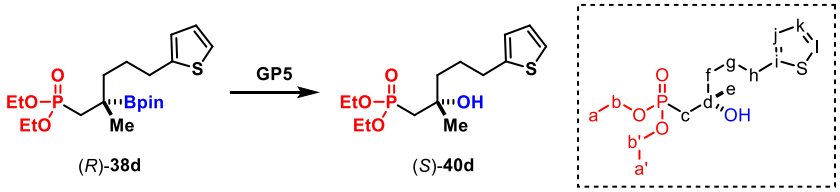


(*R*)-**38c** (*S*)-**40c**

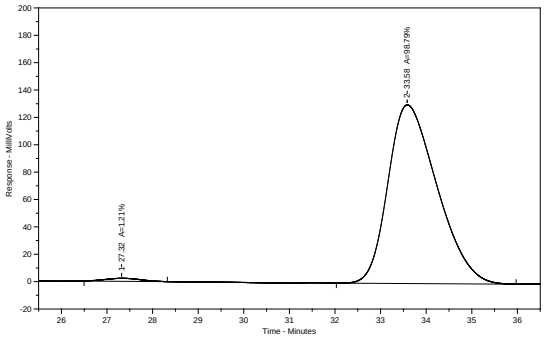
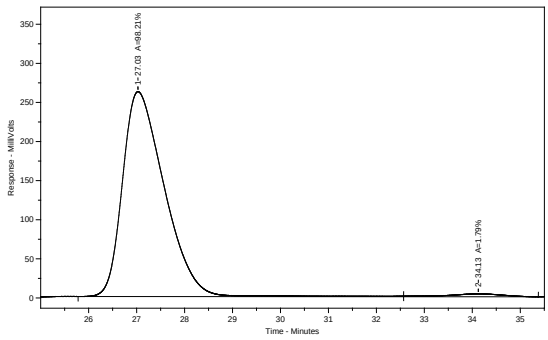
Synthesis of chiral tertiary alcohol (*S*)-**40c:** Following the general procedure for oxidation of chiral tertiary boronic esters **GP5**, the chiral tertiary boronic ester (*R*)-**38c** (60 mg, 0.13 mmol) yields the chiral tertiary alcohol (*S*)-**40c** (42, 93%) as a colorless viscous oil: TLC analysis (7:3 ethyl acetate : hexanes) R_f = 0.5; $[\alpha]_D^{20}$ = +7.8° (*c* = 1.0, $CHCl_3$); ^{1}H

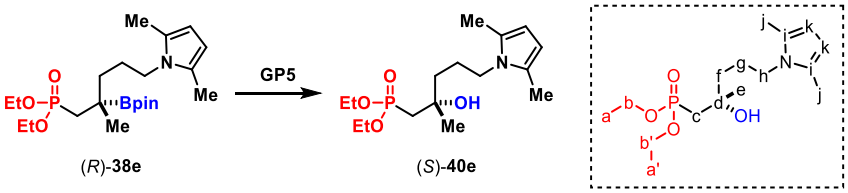
NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.4 Hz, k), 7.13 (2H, d, *J* = 8.4 Hz, j), 4.18-4.07 (4H, m, b+b'), 3.94 (1H, s, OH), 2.61 (2H, t, *J* = 7.4 Hz, h), 2.07-1.92 (2H, m, c), 1.75-1.59 (4H, m, f+g), 1.40-1.30 (9H, m, a+a'+e) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.84 (i), 131.59 (l), 129.85 (j), 128.50 (k), 70.50 (d, $^{2}J_{C\text{-}P}$ = 5 Hz, d), 61.77 (d, $^{2}J_{C\text{-}P}$ = 7 Hz, b+b'), 43.07 (d, $^{3}J_{C\text{-}P}$ = 12 Hz, f), 37.39 (d, $^{1}J_{C\text{-}P}$ = 134 Hz, c), 35.62 (h), 28.11 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, e), 26.00 (g), 16.55-16.47 (m, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.04 ppm; IR (neat) 3410 (O-H), 2980 (aromatic C-H), 2865 (aliphatic C-H), 1492, 1391, 1220 (P=O), 1051 (C-O), 1023 (C-O), 958 (P-O), 818 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{26}ClO_4P+Na^+$ 371.1149, found 371.1157 *m/z*. Enantiomer ratio = 99:1, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 1:1 isopropanol:hexanes; Flow rate = 0.5 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a). R:S = 1:99, CAHB of **37c** with (*R*,*R*)-**T2**, then oxidation:	(b). Racemate:
	



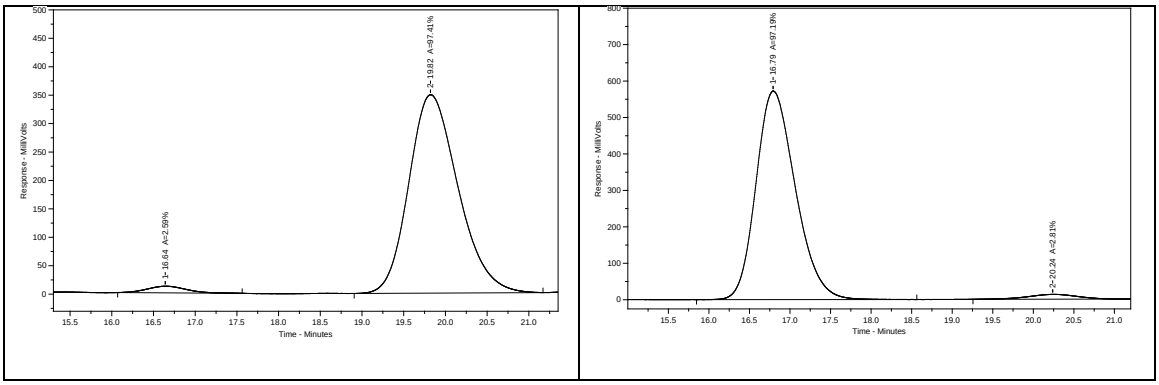
Synthesis of chiral tertiary alcohol (*S*)-**40d:** Following the general procedure for oxidation of chiral tertiary boronic esters **GP5**, the chiral tertiary boronic ester (*R*)-**38d** (56 mg, 0.13 mmol) yielded the chiral tertiary alcohol (*S*)-**40d** (38 mg, 91%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = +1.2° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.12 (1H, dd, *J* = 5.1, 1.2 Hz, l), 6.94-6.91 (1H, m, k), 6.82-6.80 (1H, m, j), 4.17-4.07 (4H, m, b+b'), 3.95 (1H, s, OH), 2.86 (2H, t, *J* = 7.2 Hz, h), 2.06-1.92 (2H, m, c), 1.82-1.65 (4H, m, f+g), 1.38-1.33 (9H, m, a+a'+e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.18 (i), 126.71 (j), 124.17 (k), 122.93 (l), 70.43 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 61.68 (d, $^2J_{C\text{-}P}$ = 6.75 Hz, b+b'), 42.89 (d, $^3J_{C\text{-}P}$ = 11.25 Hz, f), 37.25 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 30.20 (h), 28.00 (d, $^3J_{C\text{-}P}$ = 9.75 Hz, e), 26.49 (g), 16.40 (d, $^3J_{C\text{-}P}$ = 6.75 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.05 ppm; IR (neat) 3408 (O-H), 2979 (aromatic C-H), 2907 (aliphatic C-H), 2165, 2028, 1741, 1468, 1371, 1220 (P=O), 1145 (C-O), 1021 (C-O), 958 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{25}O_4PS$ 320.1211, found 320.1203 *m/z*. Enantiomer ratio = 98.5:1.5, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 3:2 isopropanol:hexanes; Flow rate = 1.5 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

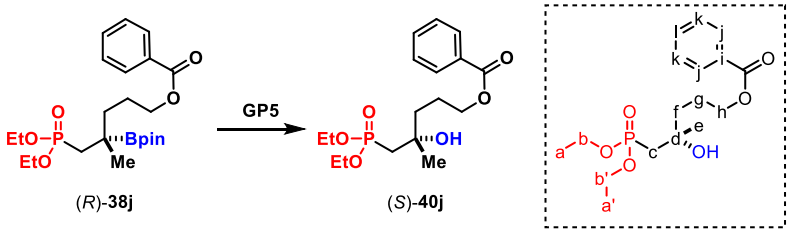
(a). R:S = 1:99, CAHB of **37d** with (*R*,*R*)-**T2**, then oxidation:	(b). R:S = 98:2, CAHB of **37d** with (*S*,*S*)-**T2**, then oxidation:
	



Synthesis of chiral tertiary alcohol (*S*)-**40e:** Following the general procedure for oxidation of chiral tertiary boronic esters **GP5**, the chiral tertiary boronic ester (*R*)-**38e** (57 mg, 0.13 mmol) yielded the chiral tertiary alcohol (*S*)-**40e** (31 mg, 73%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = +5.8° (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (2H, s, k), 4.18-4.07 (4H, m, b+b'), 3.78-3.74 (2H, m, h), 2.44 (6H, s, j), 2.09-1.90 (2H, m, c), 1.79-1.60 (5H, m, f+g+OH), 1.38-1.34 (9H, m, a+a'+e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.27 (i), 105.11 (k), 70.21 (d, $^2J_{C\text{-}P}$ = 5.25 Hz, d), 61.77 (d, $^2J_{C\text{-}P}$ = 6 Hz, b+b'), 43.73 (h), 40.33 (d, $^3J_{C\text{-}P}$ = 11.25 Hz, f), 37.24 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 27.99 (d, $^3J_{C\text{-}P}$ = 9.75 Hz, e), 25.79 (g), 16.47-16.35 (m, a+a'), 12.55 (j) ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.86 ppm; IR (neat) 3348 (O-H), 2977 (sp^2 C-H), 2940 (sp^3 C-H), 1370 (C=N), 1241 (P=O), 1051 (C-O), 1023 (C-O), 953 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{30}NO_4P$ 331.1912, found 331.1905 *m/z*. Enantiomer ratio = 97:3, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = isopropanol; Flow rate = 1 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

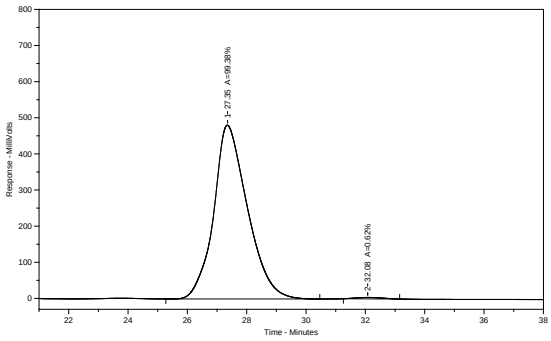
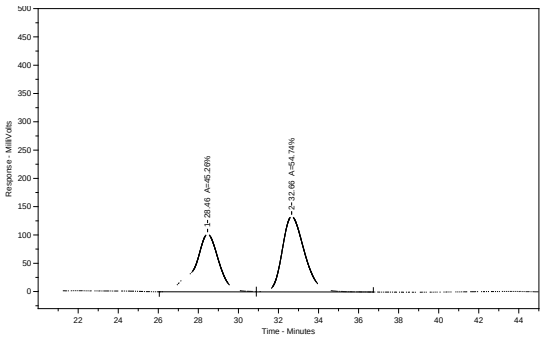
(a). R:S = 3:97, CAHB of **37e** with (*R*,*R*)-**T2**, then oxidation:	(b). R:S = 97:3, CAHB of **37e** with (*S*,*S*)-**T2**, then oxidation:

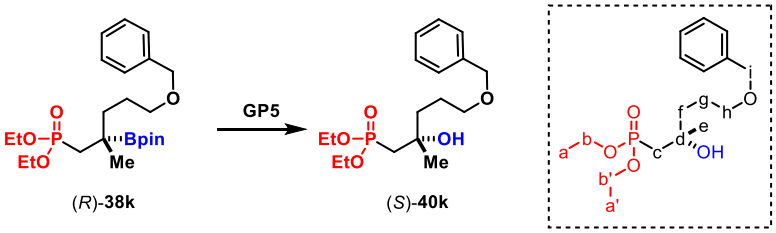




Synthesis of chiral tertiary alcohol (*S*)-**40j:** Following the general procedure for oxidation of chiral tertiary boronic esters **GP5**, the chiral tertiary boronic ester (*R*)-**38j** (46.8 mg, 0.10 mmol) yielded the chiral tertiary alcohol (*S*)-**40j** (34 mg, 95%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = +2.5º (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.04 (2H, m, j), 7.58-7.55 (1H, m, l), 7.47-7.43 (2H, m, k), 4.36 (2H, t, *J* = 6.6 Hz, h), 4.19-4.08 (4H, m, b+b'), 4.08 (1H, s, OH), 2.12-1.71 (6H, m, c+f+g), 1.38-1.31 (9H, m, a+a'+e) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.69 (carbonyl C), 132.98 (l), 130.47 (i), 129.65 (j), 128.44 (k), 70.30 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 65.27 (h), 61.84 (dd, $^2J_{C\text{-}P}$ = 6.0 Hz, b+b'), 39.85 (d, $^3J_{C\text{-}P}$ = 12 Hz, f), 37.47 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 28.08 (d, $^3J_{C\text{-}P}$ = 9 Hz, e), 23.73 (g), 16.49 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.81 ppm; IR (neat) 3370 (O-H), 2979 (aromatic C-H), 2905 (aliphatic C-H), 1717 (C=O), 1452, 1371, 1273 (P=O), 1023 (C-O), 957 (P-O), 712 cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{27}O_6P$+Na^+ 381.1437, found 381.1444 *m/z*. Enantiomer

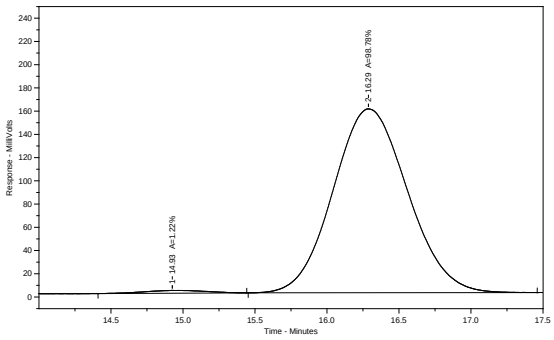
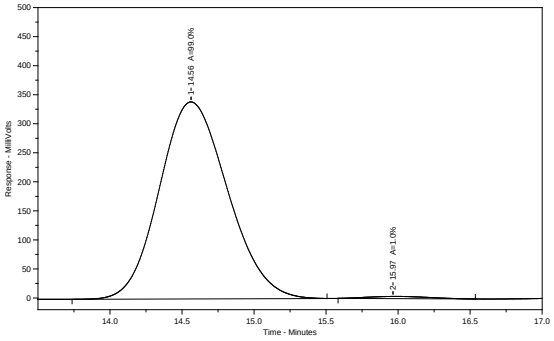
ratio = >99:1, determined via chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = isopropanol; Flow rate = 1 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

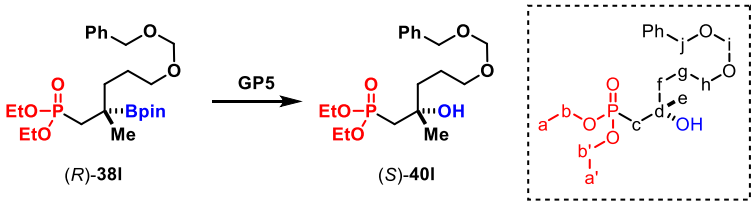
(a). R:S = 0.6 : 99.4, CAHB of **37j** with (*R*,*R*)-**T2**, then oxidation:	(b). Racemate
	



Synthesis of chiral tertiary alcohol (*S*)-**40k:** Following the general procedure for oxidation of chiral tertiary boronic esters **GP5**, the chiral tertiary boronic ester (*R*)-**38k** (45 mg, 0.10 mmol) yields the chiral tertiary alcohol (*S*)-**40k** (33 mg, 95%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = –1.05° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.25 (5H, m, aryl), 4.52 (2H, s, i), 4.21-4.05 (4H, m, b+b'), 4.01 (1H, s, OH), 3.51 (2H, t, *J* = 7.0 Hz, h), 2.12-1.93 (2H, m, c), 1.73-1.70 (4H, m, f+g), 1.37-1.31 (9H, m, a+a'+e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.47 (aryl), 128.36 (aryl), 127.65 (aryl), 127.54 (aryl), 72.94 (i), 70.65 (h), 70.34 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 61.54 (d, $^2J_{C\text{-}}$

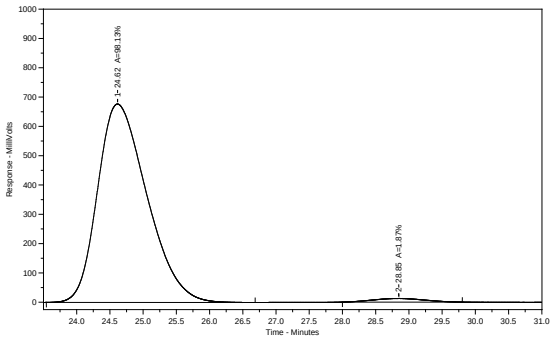
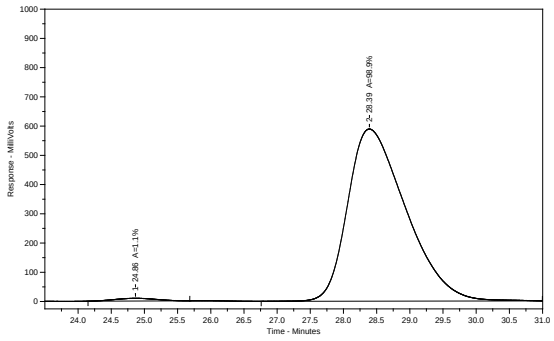
$_P$ = 9.0, 6.0 Hz Hz, b+b'), 40.11 (d, $^3J_{C\text{-}P}$ = 11.25 Hz, f), 37.30 (d, $^1J_{C\text{-}P}$ = 131 Hz, c), 28.01 (d, $^3J_{C\text{-}P}$ = 9 Hz, e), 24.58 (g), 16.38 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.95 ppm; IR (neat) 3439 (O-H), 2978 (C-H), 2117, 1790, 1454, 1371, 1316, 1214 (P=O), 1144, 1052 (C-O), 1023 (C-O), 956 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{29}O_5P$ 344.1753, found 344.1766 *m/z*. Enantiomer ratio = 99:1, determined via chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = isopropanol; Flow rate = 1.5 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

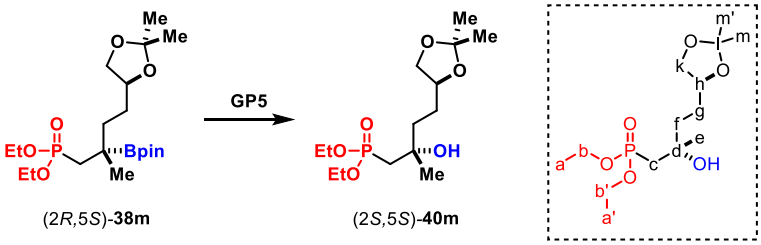
(a). R:S = 1:99, CAHB of **37k** with (*R*,*R*)-**T2**, then oxidation:	(b). R:S = 99:1, CAHB of **37k** with (*S*,*S*)-**T2**, then oxidation:
	



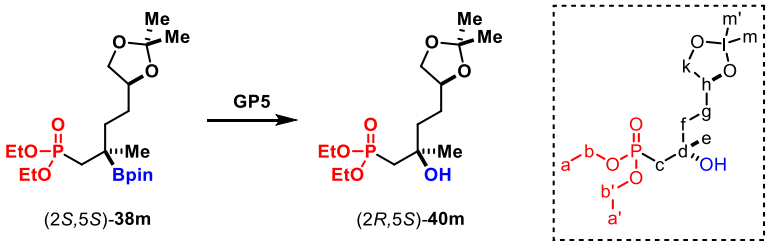
Synthesis of chiral tertiary alcohol (*S*)-**40l:** Following the general procedure for oxidation of chiral tertiary boronic esters **GP5** using (*R*,*R*)-**T2**, the chiral tertiary boronic ester (*R*)-**38l** (48 mg, 0.10 mmol) yields the chiral tertiary alcohol (*S*)-**40l** (35 mg, 91%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = +1.4° (*c* 1.0,

$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (5H, m, aryl), 4.77 (2H, s, j), 4.61 (2H, s, i), 4.20-4.01 (4H, m, b+b'), 3.98 (1H, s, OH), 3.64-3.60 (2H, m, h), 2.12-1.92 (2H, m, c), 1.77-1.64 (4H, m, f+g), 1.37-1.32 (9H, m, a+a'+e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.92 (aryl), 128.42 (aryl), 127.86 (aryl), 127.68 (aryl), 94.61 (j), 70.30 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 69.31 (i), 68.26 (h), 61.67 (dd, $^2J_{C\text{-}P}$ = 6.0, 3.0 Hz, b+b'), 40.11 (d, $^3J_{C\text{-}P}$ = 12 Hz, f), 38.31 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 27.98 (d, $^3J_{C\text{-}P}$ = 8.25 Hz, e), 24.47 (g), 16.39 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.96 ppm; IR (neat) 3423 (O-H), 2978 (C-H), 1758, 1454, 1375, 1223 (P=O), 1023 (C-O), 958 (P-O), 737 cm^{-1}; HRMS (ESI) calculated for $C_{18}H_{31}O_6P+Na^+$ 397.1750, found 397.1754 *m/z*. Enantiomer ratio = 98.5:1.5, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = isopropanol; Flow rate = 1 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a). R:S = 2 : 98, CAHB of **37l** with (*R*,*R*)-**T2**, then oxidation:	(b). R:S = 99:1, CAHB of **37l** with (*S*,*S*)-**T2**, then oxidation:
	



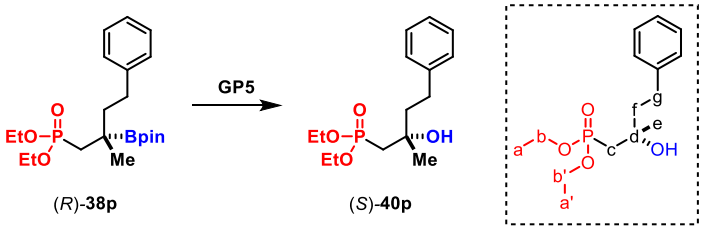
Synthesis of chiral tertiary alcohol (2*S*,5*S*)-**40m:** Following the general procedure for oxidation of chiral tertiary boronic esters **GP5**, the chiral tertiary boronic ester (2*R*,5*S*)-**38m** (57 mg, 0.13 mmol) yields the chiral tertiary alcohol (2*S*,5*S*)-**40m** (41 mg, 95%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +1.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.15-3.99 (7H, m, b+b'+k+OH), 3.53 (1H, dd, *J* = 7.7, 7.0 Hz, h), 2.05-1.93 (2H, m, c), 1.74-1.54 (4H, m, f+g), 1.39 (m or m'), 1.33-1.32 (12H, m or m' +a+a'+e) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 108.76 (l), 76.12 (h), 70.10 (d, $^2J_{C\text{-}P}$ = 5.25 Hz, d), 69.30 (k), 61.70 (dd, $^2J_{C\text{-}P}$ = 8.75, 7.00 Hz, b+b'), 39.23 (d, $^3J_{C\text{-}P}$ = 12.25 Hz, f), 37.12 (d, $^1J_{C\text{-}P}$ = 136.5 Hz, c), 28.08 (d, $^3J_{C\text{-}P}$ = 8.75 Hz, e), 28.06 (g), 26.92 (m or m'), 25.65 (m or m'), 16.37 (d, $^3J_{C\text{-}P}$ = 5.25 Hz, a+a') ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 29.82 (97%, Major diastereomer), 29.70 (3%, Minor diastereomer) ppm; IR (neat) 3399 (O-H), 2982 (C-H), 1456, 1369, 1214 (P=O), 1050 (C-O), 1022 (C-O), 958 (P-O), 837 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{29}O_6P$+Na^+ 347.1594, found 347.1604 *m/z*.



(2*S*,5*S*)-**38m** (2*R*,5*S*)-**40m**

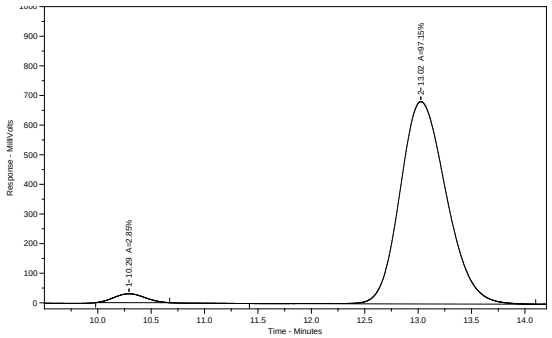
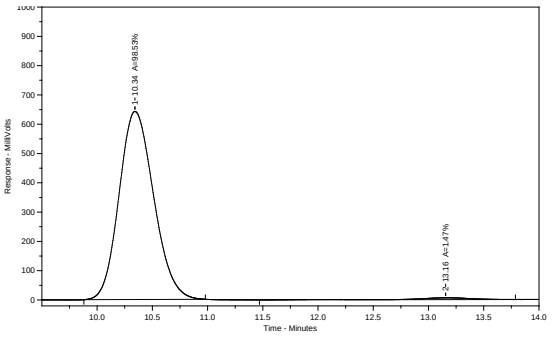
Synthesis of the tertiary alcohol (2*R*,5*S*)-**40m:** Following the general procedure for oxidation of chiral tertiary boronic esters **GP5**, the chiral tertiary boronic ester (2*S*,5*S*)-**38m** (56.5 mg, 0.13 mmol) yields the chiral tertiary alcohol (2*R*,5*S*)-**40m** (40.4 mg, 95%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +0.76° (*c* 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.15-3.99 (7H, m, b+b'+k+OH), 3.52 (1H, dd, *J* = 7.7, 7.0 Hz, h), 2.05-1.95 (2H, m, c), 1.73-1.58 (4H, m, f+g), 1.40 (m or m'), 1.33-1.32 (12H, m or m'

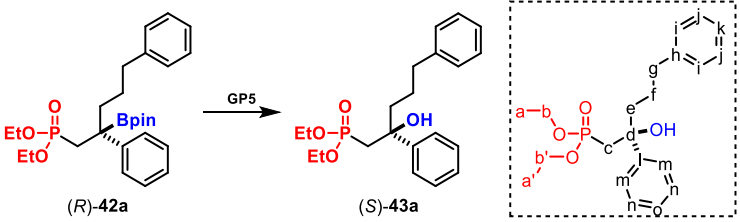
+a+a'+e) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 108.77 (l), 76.23 (h), 70.14 (d, $^{2}J_{C\text{-}P}$ = 3.5 Hz, d), 69.41 (k), 61.69 (dd, $^{2}J_{C\text{-}P}$ = 8.75, 7.00 Hz, b+b'), 39.37 (d, $^{3}J_{C\text{-}P}$ = 12.25 Hz, f), 37.45 (d, $^{1}J_{C\text{-}P}$ = 134.75 Hz, c), 28.08 (g), 27.80 (d, $^{3}J_{C\text{-}P}$ = 8.75 Hz, e), 26.92 (m or m'), 25.67 (m or m'), 16.37 (d, $^{3}J_{C\text{-}P}$ = 7 Hz, a+a') ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 29.82 (2%, Major diastereomer), 29.70 (98%, Minor diastereomer) ppm; IR (neat) 3394 (O-H), 2982 (C-H), 1456, 1369, 1214 (P=O), 1050 (C-O), 1022 (C-O), 958 (P-O), 839 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{29}O_6P$+Na^+ 347.1594, found 347.1603 *m/z*.



Synthesis of chiral tertiary alcohol (*S*)-**40p:** Following the general procedure for oxidation of chiral tertiary boronic esters **GP5** using (*R*,*R*)-**T2**, the chiral tertiary boronic ester (*R*)-**38p** (41 mg, 0.10 mmol) yielded the chiral tertiary alcohol (*S*)-**40p** (29 mg, 95%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = –5.05° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.14 (5H, m, aryl), 4.22-4.09 (4H, m, b+b'), 4.03 (1H, s, OH), 2.77-2.71 (2H, m, g), 2.19-1.87 (4H, m, c+f), 1.43 (3H, s, e), 1.40-1.32 (6H, m, a+a') ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.22 (aryl), 128.40 (aryl), 128.33 (aryl), 125.79 (aryl), 70.40 (d, $^{2}J_{C\text{-}P}$ = 5.25 Hz, d), 61.82-61.69 (m, b+b'), 45.29 (d, $^{3}J_{C\text{-}P}$ = 11.25 Hz, f), 37.35 (d, $^{1}J_{C\text{-}P}$ = 135 Hz, c), 30.44 (g), 28.07 (d, $^{3}J_{C\text{-}P}$ = 9.75 Hz, e), 16.41 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz) δ 29.98 ppm; IR (neat) 3389.56 (OH), 2978.57 (C-H), 1473.74, 1217.80 (P=O), 1147.38, 1022.88 (C-O), 953.88, 698.96 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{25}O_4P$ = 300.1490, found 300.1483 *m/z*. Enantiomer ratio

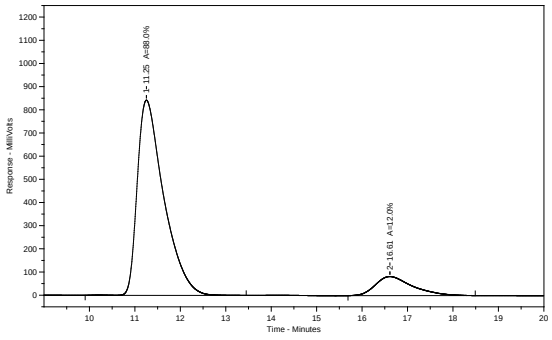
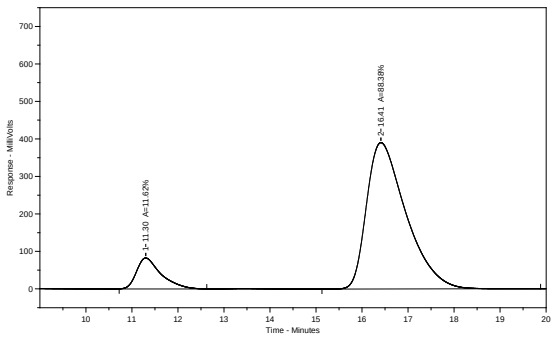
= 98:2, determined via chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = Isopropanol; Flow rate = 1.50 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

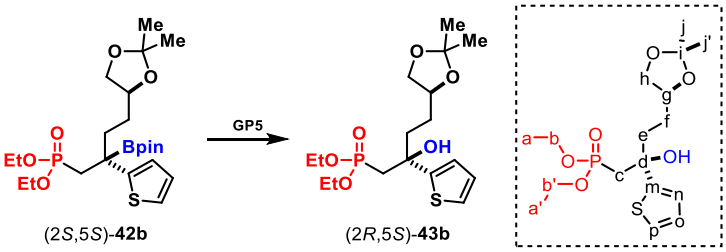
(a). R:S = 3:97, CAHB of **37p** with (*R*,*R*)-**T2**, then oxidation:	(b). R:S = 98.5:1.5, CAHB of **37p** with (*S*,*S*)-**T2**, then oxidation:
	



Synthesis of chiral tertiary benzyl alcohol (*S*)-**43a:** Following the general procedure for oxidation of chiral tertiary benzylic boronic esters (**GP5**), the chiral boronic ester (*R*)-**42a** (36 mg, 75 μmol) yields the chiral tertiary alcohol (*S*)-**43a** (25 mg, 88%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +0.8° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.09 (10H, m, aryl), 5.04 (1H, br s, OH), 4.10-3.97 (2H, m, b or b'), 3.68-3.59 (1H, m, b or b'), 3.31-3.21 (1H, m, b or b'), 2.61-2.32 (4H, m, c+g), 1.97-1.69 (3H, m, e+f(1H)), 1.41-1.29 (4H, m, a or a' + f(1H)), 0.97 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.57 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, l), 142.40

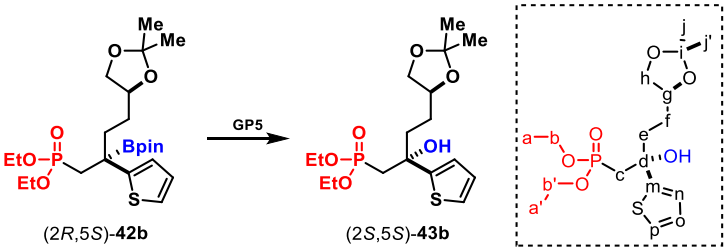
(h), 128.52 (aryl), 128.34 (aryl), 128.17 (aryl), 128.79 (aryl), 125.77 (aryl), 125.60 (aryl), 74.16 (d, $^{2}J_{C\text{-}P}$ = 5.0 Hz, d), 61.81 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.49 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 44.61 (d, $^{3}J_{C\text{-}P}$ = 15.5 Hz, e), 38.87 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 36.00 (g), 25.13 (d, $^{4}J_{C\text{-}P}$ = 2.5 Hz, f), 16.45 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.20 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.28 ppm; IR (neat) 3376 (O-H), 2985 (sp^2 C-H), 2908 (sp^3 C-H), 1451 (aromatic C=C), 1396 (aromatic C=C), 1220 (P=O), 1049 (C-O), 1021 (C-O/C=S), 965 (P-O), 729, 699 cm^{-1}. HRMS (ESI) calculated for $C_{21}H_{29}O_4P+Na^+$ = 399.1701, found 399.1706 *m/z*. Enantiomer ratio = 93:7, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AS-H; Mobile phase = 95:5 Hexanes:Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a) R:S = 12:88, CAHB of (*E*)-**41a** with (*R*,*R*)-**T2**, then oxidation to yield **43a**:	(b) R:S = 88:12, CAHB of (*E*)-**41a** with (*S*,*S*)-**T2**, then oxidation to yield **43a**:
	



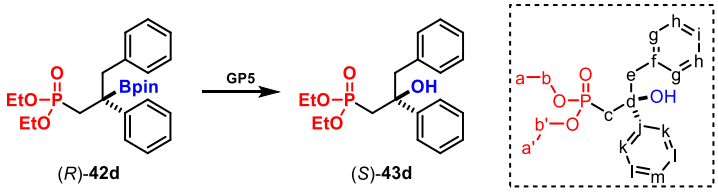
Synthesis of chiral tertiary benzyl alcohol (2*R*,5*S*)-**43b:** Following the general procedure for oxidation of chiral tertiary benzylic boronic esters (**GP5**), the chiral boronic ester (2*S*,5*S*)-**42b** (38 mg, 75 μmol; obtained via CAHB of (*Z*)-**41b** using (*R*,*R*)-**T2**) yields the chiral tertiary benzyl alcohol product (2*R*,5*S*)-**43b** (24 mg, 82%; 95:5 dr, determined via ^{31}P NMR analysis) as a light buff colored viscous oil. Alternatively, the chiral boronic ester (2*S*,5*S*)-**42b** (38 mg, 75 μmol; obtained via CAHB of (*E*)-**41b** using (*R*,*R*)-**T2**) yields the chiral tertiary benzyl alcohol product (2*R*,5*S*)-**43b** (23 mg, 80%; 95:5 dr, determined via ^{31}P NMR analysis) as a buff colored viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +10.0^o (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 6.83 (1H, dd, *J* = 5.0, 1.0 Hz, aryl), 6.81 (1H, dd, *J* = 3.5, 1.0 Hz, aryl), 6.71 (1H, dd, *J* = 5.0, 3.5 Hz, aryl), 6.21 (1H, br s, OH), 3.88-3.56 (5H, m, b+b'(total 3H)+g+h(1H)), 3.37-3.23 (2H, m, b or b'(1H)+h(1H)), 2.28 (1H, dd, *J* = 19.0, 15.0 Hz, c(1H)), 2.24 (1H, dd, *J* = 19.0, 15.0 Hz, c(1H)), 2.09 (1H, ddd, *J* = 18.0, 13.0, 5.0 Hz, e(1H)), 1.97 (1H, dd, *J* = 18.0, 13.0, 4.5 Hz, e(1H)), 1.82-1.73 (1H, m, f(1H)), 1.53-1.43 (1H, m, f(1H)), 1.34 (3H, s, j or j'), 1.29 (3H, s, j or j'), 0.98 (3H, t, *J* = 7.0 Hz, a or a'), 0.80 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 152.45 (d, $^3J_{C\text{-}P}$ = 7.5 Hz, m), 127.19 (aryl), 124.63 (aryl), 123.77 (aryl), 109.05 (i), 76.70 (g), 73.94 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 69.94 (h), 62.15 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.59 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 43.09 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, e), 40.50 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 28.66 (d, $^4J_{C\text{-}P}$ = 2.0 Hz, f), 27.64 (j or j'), 26.36 (j or j'), 16.66 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.56 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, C_6D_6) δ 28.85 (5%, minor diastereomer), 28.77 (95%, major diastereomer) ppm; IR (neat) 3377 (O-H), 2983 (aromatic C-H), 2933 (aliphatic C-H), 1443 (aromatic C=C), 1368 (aromatic C=C), 1214

(P=O), 1158, 1021 (C-O/C=S), 962 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{29}O_6PS+Na^+$ = 415.1320, found 415.1327 *m/z*.



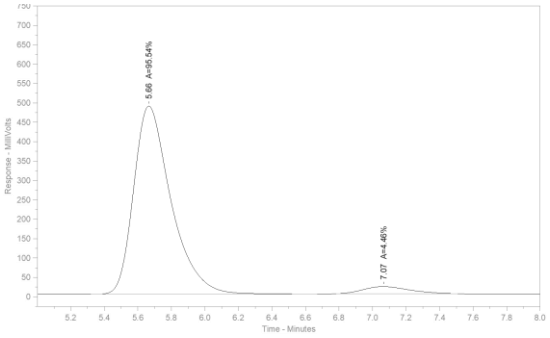
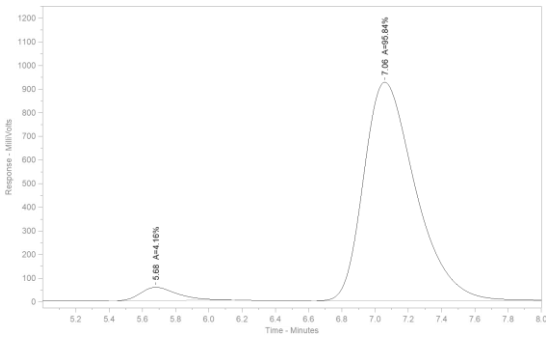
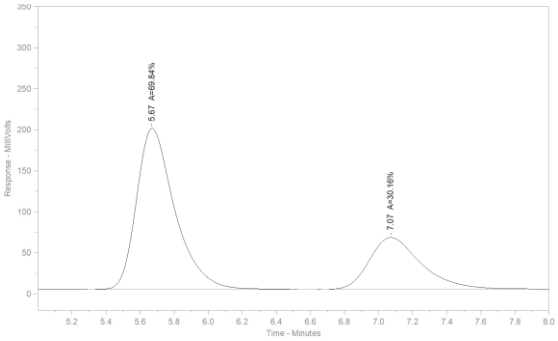
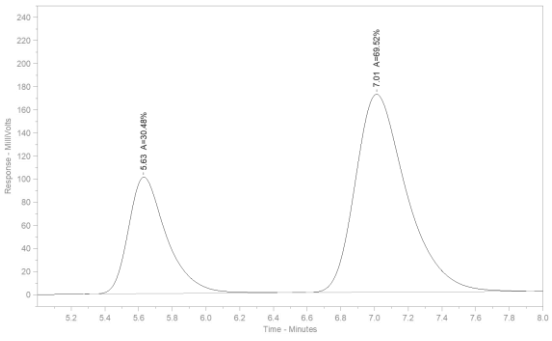
Synthesis of chiral tertiary benzyl alcohol (2*S*,5*S*)-**42b:** Following the general procedure for oxidation of chiral tertiary benzylic boronic esters (**GP5**), the chiral boronic ester (2*R*,5*S*)-**42b** (38 mg, 75 μmol; obtained via CAHB of (*Z*)-**41b** using (*S*,*S*)-**T2**) yields the chiral tertiary benzyl alcohol product (2*S*,5*S*)-**43b** (25 mg, 85%; 94:6 dr, determined via ^{31}P NMR analysis) as a light buff colored viscous oil. Alternatively, the chiral boronic ester (2*R*,5*S*)-**42b** (38 mg, 75 μmol; obtained via CAHB of (*E*)-**41b** using (*S*,*S*)-**T2**) yields the chiral tertiary benzyl alcohol product (2*S*,5*S*)-**43b** (24 mg, 82%; 95:5 dr, determined via ^{31}P NMR analysis) as a buff colored viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +3.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 6.84 (1H, dd, *J* = 5.0, 1.0 Hz, aryl), 6.80 (1H, dd, *J* = 3.5, 1.0 Hz, aryl), 6.72 (1H, dd, *J* = 5.0, 3.5 Hz, aryl), 6.21 (1H, br s, OH), 3.85-3.57 (5H, m, b+b'(total 3H)+g+h(1H)), 3.37-3.23 (2H, m, b or b'(1H)+h(1H)), 2.31-2.16 (3H, m, c+e(1H)), 1.93-1.76 (2H, m, e(1H)+f(1H)), 1.51-1.43 (1H, m, f(1H)), 1.38 (3H, s, j or j'), 1.29 (3H, s, j or j'), 0.99 (3H, t, *J* = 7.0 Hz, a or a'), 0.80 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 152.85 (d, $^3J_{C\text{-}P}$ = 7.0 Hz, m), 127.22 (aryl), 124.58 (aryl), 123.77 (aryl), 109.09 (i), 76.54 (g), 73.77 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 69.88 (h), 62.14 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.60 (d, $^2J_{C\text{-}P}$ = 6.0 Hz, b or b'), 43.08 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, e), 40.06 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 28.49 (d, $^4J_{C\text{-}P}$ = 2.0 Hz, f), 27.60 (j or

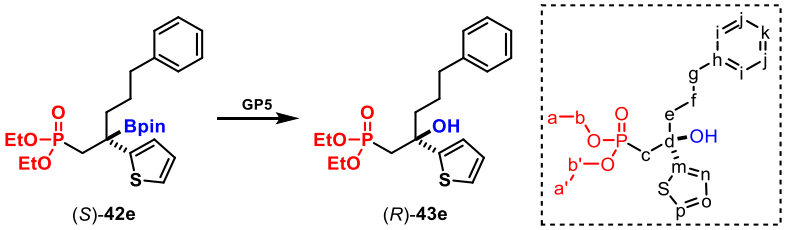
j'), 26.32 (j or j'), 16.66 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.56 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, C_6D_6) δ 28.85 (94%, minor diastereomer), 28.77 (6%, major diastereomer) ppm; IR (neat) 3378 (O-H), 2981 (aromatic C-H), 2933 (aliphatic C-H), 1445 (aromatic C=C), 1363 (aromatic C=C), 1213 (P=O), 1158, 1021 (C-O/C=S), 963 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{29}O_6PS+Na^+$ = 415.1320, found 415.1329 *m/z*.



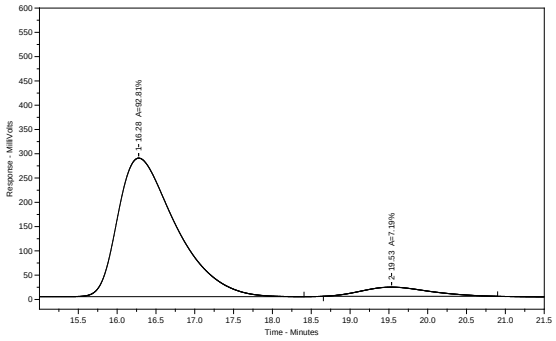
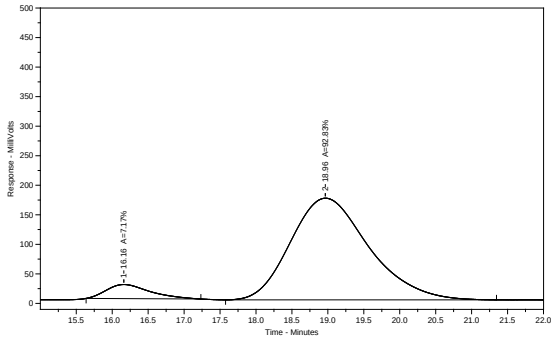
Synthesis of chiral tertiary alcohol (*S*)-**43d:** Following the general procedure for oxidation of chiral tertiary benzylic boronic esters (**GP5**), the chiral boronic ester (*R*)-**42d** (34 mg, 75 μmol; obtained via CAHB of (*E*)-**41d** using (*R,R*)-**T2**) yields the chiral tertiary benzyl alcohol product (*S*)-**43d** (21 mg, 80%; 97:3 er, determined via chiral HPLC analysis) as a light buff colored viscous oil. Alternatively, the chiral boronic ester (*R*)-**42d** (34 mg, 75 μmol; obtained via CAHB of (*Z*)-**41d** using (*R,R*)-**T2**) yields the chiral tertiary benzyl alcohol product (*S*)-**43d** (20 mg, 76%; 70:30 er, determined via chiral HPLC analysis) as a buff colored viscous oil. Characterization data for enantioenriched (*S*)-**43d**: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = -19.3° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.42-7.20 (8H, m, aryl), 7.06-7.05 (2H, m, aryl), 5.05 (1H, br s, OH), 4.04-3.96 (2H, m, b or b'), 3.66-3.57 (1H, m, b or b'), 3.25-3.04 (3H, m, b or b' (1H)+e), 2.55 (1H, dd, *J* = 19.0, 15.0 Hz, c(1H)), 2.34 (1H, dd appearing as t, *J* = 16.0 Hz, c(1H)), 1.28 (3H, t, *J* = 7.0 Hz, a or a'), 0.95 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.54 (d, $^{3}J_{C\text{-}P}$ = 4.5 Hz, j), 136.64 (f), 131.10 (aryl), 128.00 (aryl), 127.85 (aryl), 127.00 (aryl), 126.61 (aryl), 125.99 (aryl), 74.63 (d, $^{2}J_{C\text{-}P}$ = 4.5 Hz, d), 61.93 (d, $^{2}J_{C\text{-}$

$_P$ = 6.5 Hz, b or b'), 61.50 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 51.62 (d, $^3J_{C\text{-}P}$ = 17.0 Hz, e), 37.26 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 16.43 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a or a'), 16.22 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.49 ppm; IR (neat) 3398 (O-H), 2981 (sp^2 C-H), 2917 (sp^3 C-H), 1495 (aromatic C=C), 1392 (aromatic C=C), 1222 (P=O), 1022 (C-O), 967 (P-O), 728, 698 cm^{-1}. HRMS (ESI) calculated for $C_{19}H_{25}O_4P+Na^+$ = 371.1388, found 371.1393 *m/z*. Enantiomer ratio determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AS-H; Mobile phase = 90:10 Hexanes: Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

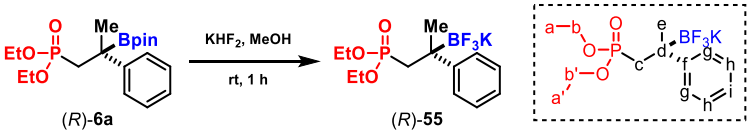
(a) R:S = 4:96, CAHB of (*E*)-**41d** with (*R*,*R*)-**T2**, then oxidation to yield **43d**: 	(b) R:S = 96:4, CAHB of (*E*)-**41d** with (*S*,*S*)-**T2**, then oxidation to yield **43d**: 
(c) R:S = 30:70, CAHB of (*Z*)-**41d** with (*R*,*R*)-**T2**, then oxidation to yield **43d**: 	(d) R:S = 70:30, CAHB of (*Z*)-**41d** with (*S*,*S*)-**T2**, then oxidation to yield **43d**: 



Synthesis of chiral tertiary benzyl alcohol (*R*)-**43e:** Following the general procedure for oxidation of chiral tertiary benzylic boronic esters (**GP5**), the chiral boronic ester (*S*)-**42e** (37 mg, 75 μmol) yields the chiral tertiary benzyl alcohol (*R*)-**43e** (25 mg, 87%) as a colorless viscous oil: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = -3.0° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.12 (6H, m, aryl), 3.96 (1H, dd, *J* = 4.5, 4.0 Hz, aryl), 6.90 (1H, d, *J* = 3.5 Hz, aryl), 5.42 (1H, br s, OH), 4.09-3.99 (2H, m, b or b'), 3.86-3.76 (1H, m, b or b'), 3.59-3.49 (1H, m, b or b'), 2.64-2.52 (2H, m, g), 2.43 (1H, dd, *J* = 22.0, 15.0 Hz, c(1H)), 2.38 (1H, dd, *J* = 22.0, 15.0 Hz, c(1H)), 2.00-1.73 (3H, m, e+f(1H)), 1.57-1.47 (1H, m, e(1H)), 1.32 (3H, t, *J* = 7.0 Hz, a or a'), 1.10 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.39 (d, $^3J_{C\text{-}P}$ = 7.5 Hz, m), 142.33 (h), 128.57 (aryl), 128.40 (aryl), 126.85 (aryl), 125.86 (aryl), 124.23 (aryl), 123.22 (aryl), 73.68 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, d), 62.14 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.67 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 45.65 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, e), 39.49 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 35.94 (g), 25.39 (d, $^4J_{C\text{-}P}$ = 2.0 Hz, f), 16.50 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a or a'), 16.35 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{13}C NMR (162 MHz, $CDCl_3$) δ 28.57 ppm; IR (neat) 3380 (O-H), 2982 (sp^2 C-H), 2908 (sp^3 C-H), 1453 (aromatic C=C), 1391 (aromatic C=C), 1217 (P=O), 1049 (C-O), 1020 (C-O/C=S), 962 (P-O), 728, 697 cm^{-1}. HRMS (ESI) calculated for $C_{19}H_{27}O_4PS+Na^+$ = 405.1265, found 405.1265 *m/z*. Enantiomer ratio = 93:7, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AS-H; Mobile phase = 95:5 Hexanes: Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

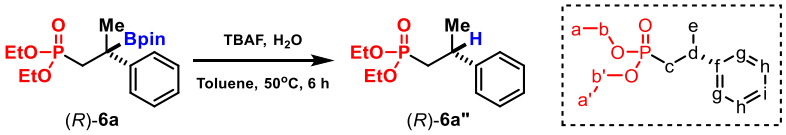
(a) R:S = 93:7, CAHB of **41e** with (*R*,*R*)-**T2**, then oxidation to yield **43e**:	(b) R:S = 7:93, CAHB of **41e** with (*S*,*S*)-**T2**, then oxidation to yield **43e**:
	

5.7. Stereospecific Functionalizations of Phosphonate-Functionalized Chiral Boronic Esters



Representative procedure for transformation of phosphonate-functionalized chiral boronic esters to the corresponding potassium trifluoroborate salts (GP6): This transformation was carried out with a slight modification of the original procedure reported procedure[16] by Aggarwal as follows: To a solution of the chiral tertiary benzylic boronic ester (*R*)-**6a** (57 mg, 0.15 mmol, 1.0 eq) in methanol (0.75 mL) was added 4.5M solution of KHF_2 in H_2O (0.15 mL, 0.67 mmol, 4.5 eq) dropwise at room temperature and the resultant mixture was stirred vigorously for 1 hour. Afterwards, the volatiles were removed under reduced pressure and the residue was redissolved in 1:1 Ethanol: Benzene (3 mL) and the mixture was evaporated in rotary evaporator to get rid of the solvents. This process was repeated 4 times to get rid of pinacol diol. To the resultant residue was added dry acetone (3 mL) and the resultant mixture was evaporated. This process was repeated 3

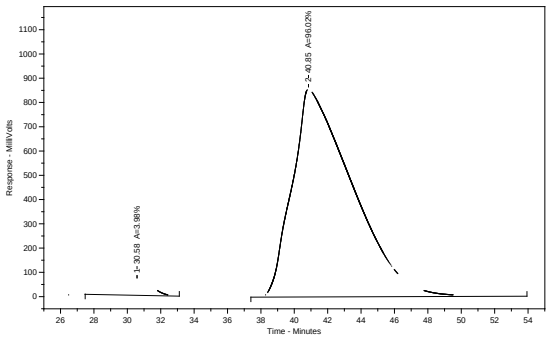
times. Finally, the resultant residue was triturated with dry acetone (3 mL x 4) and the combined organics were dried under reduced pressure to afford the potassium trifluoroborate salt (*R*)-**55** as white powder (47 mg, 87%): $[\alpha]_D^{20}$ = -21° (*c* = 1.0, CH_3CN); ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (2H, d, *J* = 8.0 Hz, g), 7.23 (2H, dd, *J* = 8.0, 7.0 Hz, h), 7.05 (2H, dd, *J* = 7.0 Hz, h), 3.88-3.56 (4H, m, b+b'), 2.62 (1H, t, *J* = 16.0 Hz, c(1H)), 2.18 (1H, t, *J* = 17.0 Hz, c(1H)), 1.45 (3H, s, e), 1.13 (3H, t, *J* = 7.0 Hz, a or a'), 1.06 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 151.29 (d, $^3J_{C\text{-}P}$ = 4.0 Hz, f), 128.07 (g+h), 124.39 (i), 61.89 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 61.87 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 34.46 (d, $^1J_{C\text{-}P}$ = 133 Hz, c), 21.09 (d, $^3J_{C\text{-}P}$ = 4.0 Hz, e), 16.55 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.49 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, CD_3OD) δ 36.04 ppm; ^{19}F NMR (376 MHz, CD_3OD) δ -153.57 ppm; ^{11}B NMR (128 MHz, CD_3OD) δ 4.87 (br, s) ppm; IR (neat) 2983 (aromatic C-H), 2909 (aliphatic C-H), 1599, 1442 (aromatic C=C), 1409 (aromatic C=C), 1280 (P=O), 1187, 1056 (C-O), 1005 (C-O), 967, 856, 823, 791, 700 cm^{-1}. HRMS (ESI) calculated for $C_{13}H_{20}BF_3KO_3P+K^+$ = 401.0469, found 401.0459 *m/z*.



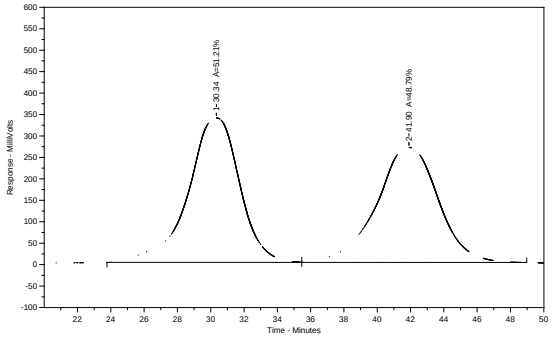
Representative procedure for protodeboronation of chiral tertiary benzylic boronic esters to the corresponding chiral reduced products (GP7): This transformation was carried out according to the procedure reported[17] by Aggarwal as follows. To a solution of the chiral tertiary benzylic boronic ester (*R*)-**6a** (57 mg, 0.15 mmol, 1.0 eq) in toluene (0.75 mL) was added tetrabutylammonium fluoride (TBAF, 0.3 mL; 1M solution in THF) and the resultant mixture was vigorously stirred at 50°C for 6 hours. (Note: Commercial TBAF is contaminated with up to 5% H_2O and hence addition of water separately was not

necessary). Afterwards, the reaction mixture was concentrated and purified by flash chromatography on silica gel (ethyl acetate) to afford the chiral reduced product (*R*)-**6a"** as a colorless oil (33 mg, 85%): TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +15.9 º (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (5H, m, aryl), 4.08-3.87 (4H, m, b+b'), 3.29-3.17 (1H, m, d), 2.21-1.96 (2H, m, c), 1.41 (3H, d, *J* = 7.0 Hz, e), 1.26 (3H, t, *J* = 7.0 Hz, a or a'), 1.22 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.90 (d, $^3J_{C\text{-}P}$ = 12.0 Hz, f), 128.68 (g or h), 126.85 (g or h), 126.56 (i), 61.56 (d, $^2J_{C\text{-}P}$ = 7.0 Hz, b or b'), 61.39 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 34.87 (d, $^2J_{C\text{-}P}$ = 3.5 Hz, d), 34.48 (d, $^1J_{C\text{-}P}$ = 138.5 Hz, c), 23.71 (d, $^3J_{C\text{-}P}$ = 9.0 Hz, e), 16.52 (d, $^3J_{C\text{-}P}$ = 7.0 Hz, a or a'), 16.51 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.16 ppm; IR (neat) 2978 (aromatic C-H), 2905 (aliphatic C-H), 1453 (aromatic C=C), 1391 (aromatic C=C), 1246 (P=O), 1053 (C-O), 1022 (C-O), 953 (P-O), 699 cm^{-1}; Enantiomer ratio = 96:4, determined by chiral HPLC analysis: Stationary phase = CHIRALCEL OJ-H; Mobile Phase = 97:3 Hexanes:Isopropanol; Flow rate = 1.25 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a) R:S = 96:4, CAHB of **5a** with (*R*,*R*)-**T2**, then protodeboronation:

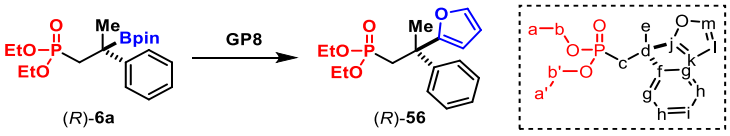


(b) Racemate:



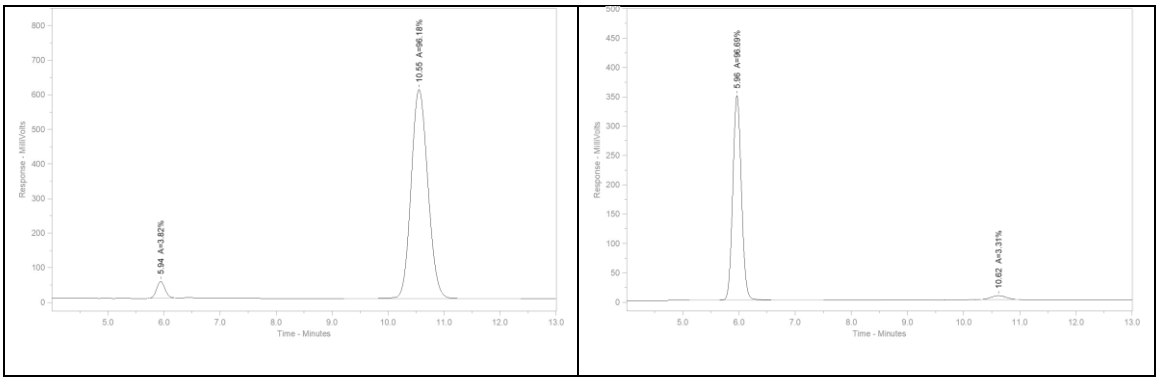
Representative procedure for the cross coupling of chiral tertiary benzylic boronic esters with furan/derivatives (GP8): This procedure is carried out with slight modifications of the original procedure[18] reported by Aggarwal and coworkers as follows. A solution of furan (2.5 equiv.) in THF (1.5 ml/0.5 mmol furan) was cooled to -78 ^{o}C using a dry ice-acetone bath and a solution of *n*BuLi in hexanes is added dropwise (2.5 equiv.). The resultant mixture is stirred at -78 ^{o}C for 30 minutes, warmed to 0 ^{o}C for 30 minutes and then cooled to -78 ^{o}C again. The phosphonate-functionalized chiral boronic ester (1.0 equiv.) in THF (1.5 mL/0.5 mmol) is added dropwise to the solution of furan-2-yl-lithium and the resultant mixture is stirred at -78 ^{o}C for 1.5 hours. Afterwards, a solution of NBS (2.5 equiv.) in THF (1.5 mL/0.5 mmol) is added dropwise and the resultant mixture stirred at room temperature for 1.5 hours. A saturated solution of $Na_2S_2O_3$ (5 mL) is added and the reaction mixture is allowed to warm up to room temperature and stirred for a total of 1 hour. The resultant mass was extracted with 1:1 ethyl acetate:diethyl-ether and the combined organic extracts are washed with brine, dried over Na_2SO_4 and concentrated in vacuum. Purification is carried out by flash chromatography over silica gel (ethyl acetate/hexanes). [*Tips & Tricks: It is common to see the appearance of minor brominated side products in the ^{31}P-NMR spectrum (bromination of the coupled furan ring occurs under reaction conditions: 5-10%) which cannot be separated from the desired cross-coupling product in chromatography. To solve this problem, the mixture post-chromatography is dissolved in dry THF under N_2, cooled to –78^{o}C and 1 eq. of nBuLi is added (ascertaining lithium-halogen exchange). The resultant mixture is stirred for 1 hour*

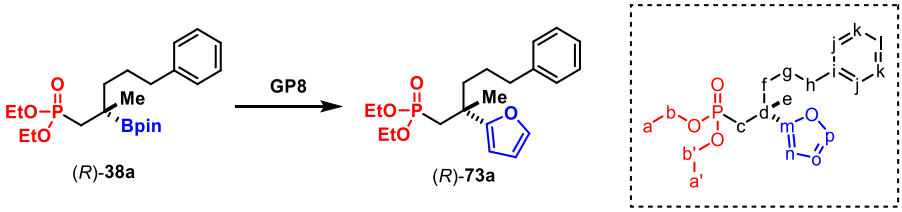
at –78°C and then quenched with the addition of water. Post-workup, the desired product is obtained in high purity.]



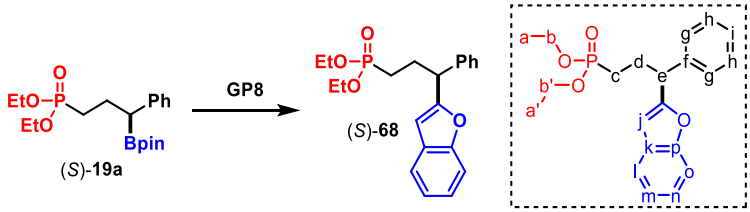
Cross-coupling of chiral tertiary benzylic boronic ester (*R*)-6a with furan: This transformation is carried out according to GP8. The chiral tertiary benzylic boronic ester (*R*)-**6a** (57 mg, 0.15 mmol, 1.0 eq) affords the coupling product (*R*)-**56** (44 mg, 91%) as a light-yellow oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +4.1 ° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.19 (6H, m, g+h+i+m), 6.33 (1H, dd, *J* = 3.0, 2.0 Hz, l), 6.20 (1H, d, *J* = 3.0 Hz, k), 3.97-3.72 (4H, m, b+b'), 2.79-2.59 (2H, m, c), 1.93 (3H, s, e), 1.18 (3H, t, *J* = 7.0 Hz, a or a'), 1.16 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.14 (d, $^3J_{C\text{-}P}$ = 12.0 Hz, j), 146.59 (d, $^3J_{C\text{-}P}$ = 12.0 Hz, f), 141.56 (m), 128.36 (g or h), 126.64 (i), 126.26 (g or h), 110.15 (l), 105.83 (k), 61.35 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 41.49 (d, $^2J_{C\text{-}P}$ = 2.0 Hz, d), 36.97 (d, $^1J_{C\text{-}P}$ = 141 Hz, c), 26.16 (d, $^3J_{C\text{-}P}$ = 2.0 Hz, e), 16.42 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.52 ppm; IR (neat) 2920 (aromatic C-H), 2853 (aliphatic C-H), 1715, 1496 (aromatic C=C), 1445 (aromatic C=C), 1240 (P=O), 1054 (C-O), 1024 (C-O), 956 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{17}H_{23}O_4P+Na^+$ = 345.1232, found = 345.1235 *m/z*. Enantiomer ratio = 97.5:3.5, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC (3 micron); Mobile Phase = 80:20 Hexanes:Isopropanol; Flow rate = 1.0 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a) R:S = 96:4, CAHB of **5a** with (*R*,*R*)-**T2**, then coupling:	(b) R:S = 3:97, CAHB of **5a** with (*S*,*S*)-**T2**, then coupling:



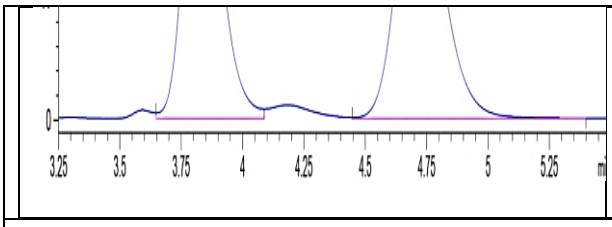


Cross-coupling of chiral tertiary boronic ester (*R*)-38a with furan: This transformation is carried out according to GP8. The chiral tertiary boronic ester (*R*)-**38a** (85 mg, 0.2 mmol, 1.0 eq) affords the coupling product (*R*)-**73a** (52 mg, 71%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 3:1) R_f = 0.6; $[\alpha]_D^{20}$ = +1.67° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.12 (6H, aryl, j+k+l+p), 6.27 (1H, dd, *J* = 3.2, 1.6 Hz, o), 6.03 (1H, dd, *J* = 3.2, 0.4 Hz, n), 4.00-3.89 (4H, m, b+b'), 2.55 (2H, t, *J* = 7.6 Hz, h), 2.29-2.09 (2H, m, c), 1.89-1.77 (2H, m, f), 1.53-1.49 (1H, m, g), 1.49 (3H, s, e), 1.35-1.28 (1H, m, g), 1.28-1.21 (6H, m, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.23 (d, $^3J_{C\text{-}P}$ = 10 Hz, m), 142.49 (i), 140.97 (p), 128.45 (j), 128.34 (k), 125.79 (l), 109.97 (o), 104.85 (n), 61.31-61.19 (dd, $^2J_{C\text{-}P}$ = 6 Hz, b+b'), 41.44 (d, $^3J_{C\text{-}P}$ = 12 Hz, f), 37.29 (d, $^2J_{C\text{-}P}$ = 2 Hz, d), 36.58 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 36.20 (h), 26.29 (g), 23.70 (d, $^3J_{C\text{-}P}$ = 4 Hz, e), 16.48 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.43 ppm; IR (neat) 2978 (aromatic C-H), 2864 (aliphatic C-H), 1602 (furan C=C), 1243 (P=O), 1054 (C-O), 1025 (C-O), 955 (P-O) cm^{-1}.



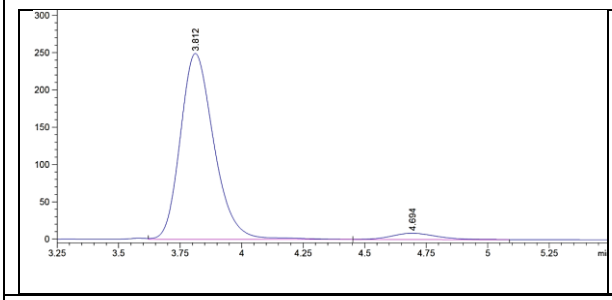
Cross-coupling of chiral secondary benzylic boronic ester (*S*)**-6a with benzofuran:** This transformation is carried out according to **GP8**. The chiral secondary benzylic boronic ester (*R*)-**19a** (95 mg, 0.25 mmol, 1.0 eq) affords the coupling product (*S*)-**68** (63 mg, 68%) as a light yellow oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -15° (*c* = 1.0, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 7.51 (1H, d, *J* = 7.5 Hz, l or o), 7.42 (1H, d, *J* = 8.0 Hz, l or o), 7.36-7.33 (4H, m, aryl), 7.29-7.19 (3H, m, aryl), 6.51 (1H, s, j), 4.15-4.07 (5H, m, b+b'+e), 2.55 (1H, br s, d(1H)), 2.30 (1H, br s, d(1H)), 1.83-1.72 (2H, m, c), 1.34 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.98 (aryl), 155.02 (aryl), 140.92 (aryl), 128.96 (aryl), 128.20 (aryl), 127.39 (aryl), 123.82 (aryl), 122.81 (aryl), 120.78 (aryl), 111.24 (aryl), 103.17 (j), 61.81 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 46.31 (d, $^3J_{C\text{-}P}$ = 17.5 Hz, e), 27.52 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, d), 24.16 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 16.68 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.47 ppm; IR (neat) 2980 (C-H), 2232, 1716, 1454, 1230 (P=O), 1024 (C-O), 957 (P-O), 726, 699, 644 cm^{-1}; HRMS (ESI) calculated for $C_{21}H_{25}O_4P+Na^+$ = 395.1388, found 395.1392 *m/z*. Enantiomer ratio = 96:4, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 60:40 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate:



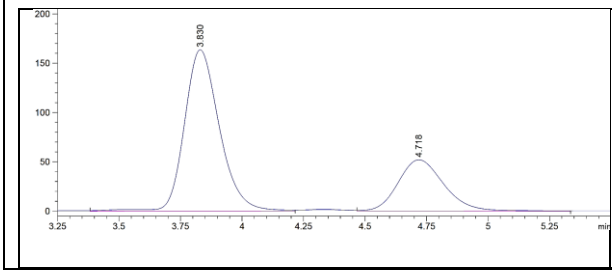
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	3.827	VV	0.1469	1480.80908	49.9775
2	4.714	VB	0.1955	1482.14026	50.0225

(b) R:S = 4:96, CAHB of (*E*/Z)-**18a** using (*R*)-**B2** followed by cross-coupling to form **68**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	3.812	VV	0.1458	2368.21924	95.6756
2	4.694	VB	0.1965	107.04126	4.3244

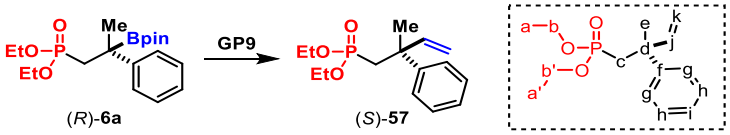
(c) R:S = 29:71, CAHB of (*E*/*Z*)-**18a** using (*R*)-**B2** followed by cross-coupling using Crudden's Conditions with 2-iodobenzofuran to obtain **68** (**GP15**; *vide infra*):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	3.830	BV	0.1519	1626.69202	70.7161
2	4.718	VB	0.2001	673.62311	29.2839

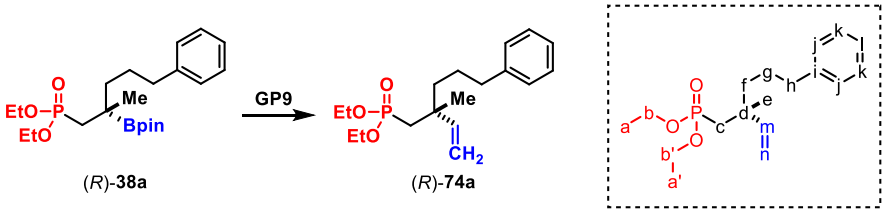
Representative procedure for vinylation of phosphonate-functionalized chiral boronic esters to the corresponding vinylated derivative (GP9): The transformation is carried out using slight modification of the original procedure[19] reported by Aggarwal and co-workers as follows. To a solution of the chiral boronic ester (1.00 eq) in anhydrous THF (10 mL/1 mmol) at –78^{o}C was added a 1*M* solution of vinyl magnesium bromide in THF (6.00 equiv.) dropwise. The reaction mixture is allowed to warm up to room temperature and stirred for a total of 2 hours. The reaction mass is cooled to – 78^{o}C and a solution of I_2

(6.00 equiv.) in methanol (2.5 mL/1 mmol) is added dropwise. The resultant mixture is stirred at -78 ^{o}C for a total of 2 hours, following which, a suspension of sodium methoxide (10 equiv.) in methanol (1.5 mL/1 mmol) is added and the reaction mixture is warmed up to room temperature and stirred for a total of 2 hours. The reaction mixture is quenched with aqueous $Na_2S_2O_3$ (sat.) and the phases are separated. The aqueous phase is extracted with 1:1 ethyl acetate : diethyl ether and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Purification is carried out using flash chromatography over silica gel.

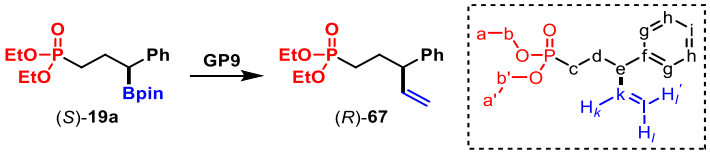


Vinylation of the tertiary benzylic boronic ester (*R*)-6a: This transformation was carried out according to **GP9**. The chiral tertiary benzylic boronic ester (*R*)-**6a** (57 mg, 0.15 mmol, 1.0 eq) affords the vinylated product (*S*)-**57** (30 mg, 71%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -7.1 ^{o} (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, d, *J* = 8.0 Hz, g), 7.31 (2H, dd, *J* = 8.0, 7.0 Hz, h), 7.20 (1H, t, *J* = 7.0 Hz, i), 6.16 (1H, dd, *J* = 17.0, 11.0 Hz, j), 5.13 (1H, d, *J* = 11.0 Hz, k(1H)), 5.08 (1H, d, *J* = 17.0 Hz, k(1H)), 3.98-3.67 (4H, m, b+b'), 2.43-2.26 (2H, m, c), 1.67 (3H, s, e), 1.19 (3H, t, *J* = 7.0 Hz, a or a'), 1.13 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.70 (d, $^{3}J_{C\text{-}P}$ = 12.0 Hz, j), 146.25 (d, $^{3}J_{C\text{-}P}$ = 8.5 Hz, f), 128.24 (h), 126.77 (g), 126.41 (i), 111.85 (k), 61.25 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz, b or b'), 61.20 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 42.37 (d, $^{2}J_{C\text{-}P}$ = 2.0 Hz, d), 37.94 (d, $^{1}J_{C\text{-}P}$ = 140 Hz, c), 25.97 (d, $^{3}J_{C\text{-}P}$ = 5.0 Hz, e), 16.45 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.39 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.47 ppm; IR (neat) 2978 (sp^2 C-H), 2905 (sp^3 C-H), 1635 (C=C), 1600 (C=C), 1494 (aromatic

C=C), 1445 (aromatic C=C), 1391 (aromatic C=C), 1238 (P=O), 1054 (C-O), 1024 (C-O), 954 (P-O), 698 cm^{-1}; Enantiomer ratio = 97:3, Determined from derivatives obtained via oxophosphonate intermediate **61**.

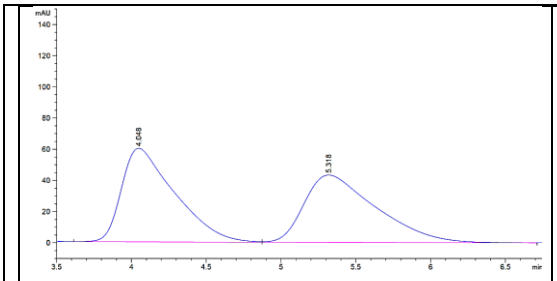


Vinylation of the chiral tertiary boronic ester (*R*)-**38a:** This transformation was carried out according to **GP9**. The chiral tertiary benzylic boronic ester (*R*)-**38a** (424 mg, 1.00 mmol, 1.00 eq) affords the vinylated product (*S*)-**38a** (302 mg, 93%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 3:1) R_f = 0.6; $[\alpha]_D^{20}$ = +1.12 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.16 (5H, m, aryl), 5.85 (1H, dd, *J* = 10.8, 6.4 Hz, m), 5.03-4.94 (2H, m, n), 4.11-4.03 (4H, m, b+b'), 2.59 (2H, br, h), 1.85 (2H, d, *J* = 18.8 Hz), 1.58-1.55 (4H, m, f+g), 1.31 (6H, t, *J* = 7.1 Hz, a+a'), 1.21 (3H, s, e); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.20 (d, $^3J_{C\text{-}P}$ = 10 Hz, m), 142.64 (i), 128.48 (aryl), 128.37 (aryl), 125.79 (aryl), 111.85 (n), 61.34-61.17 (m, b+b'), 41.40 (d, $^3J_{C\text{-}P}$ = 9 Hz, f), 38.27 (d, $^2J_{C\text{-}P}$ = 2 Hz, d), 36.87 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 36.51 (h), 26.37 (g), 24.14 (d, $^3J_{C\text{-}P}$ = 6 Hz, e), 16.54 ($^3J_{C\text{-}P}$ = 6 Hz, a+a'); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.62 ppm; IR (neat) 3025.69 (sp^2 C-H), 2904.16 (sp^3 C-H), 1636.80 (C=C), 1242.06 (P=O) cm^{-1}; HRMS (ESI) calculated for $C_{18}H_{29}O_3P+Na^+$ 347.1747, found 347.1756 *m/z*. Enantiomer ratio = 98:2 (obtained from the derivatives **78a** and **79a**).



Vinylation of the chiral tertiary boronic ester (*S*)-**19a:** This transformation was carried out according to **GP9**. The chiral tertiary benzylic boronic ester (*S*)-**19a** (76 mg, 0.2 mmol, 1.0 eq) affords the vinylated product (*R*)-**67** (44.5 mg, 79%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = -11.5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (2H, m, aryl), 7.23-7.18 (3H, m, aryl), 5.98-5.89 (1H, m, k), 5.10-5.06 (2H, m, l), 4.14-4.00 (4H, m, b+b'), 7.54 (1H, dt, *J* = 7.5 Hz, e), 2.10-1.93 (2H, m, d), 1.81-1.55 (2H, m, c), 1.31 (3H, t, *J* = 7.0 Hz, a or a'), 1.30 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1750 (f), 141.14 (k), 128.77 (aryl), 127.72 (aryl), 126.70 (aryl), 115.20 (l), 61.60 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 50.48 (d, $^3J_{C\text{-}P}$ = 17.5 Hz, e), 28.07 (d, $^2J_{C\text{-}P}$ = 4.2 Hz, d), 23.99 (d, $^1J_{C\text{-}P}$ = 141.39 Hz, c), 16.60 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.20 ppm; IR (neat) 2982 (sp^2 C-H), 2905 (sp^3 C-H), 1636 (C=C), 1600 (C=C), 1492 (aromatic C=C), 1452 (aromatic C=C), 1391 (aromatic C=C), 1240 (P=O), 1055 (C-O), 1024 (C-O), 954 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{23}O_3P+Na^+$ = 305.1283, found 305.1284 *m/z*. Enantiomer ratio = 95:5, determined by chiral HPLC analysis (**Note:** *The enantiomers of vinylated product **67** are not separable in chiral HPLC. Instead, **67** is treated with BH_3 and H_2O_2 to obtain the alcohol derivative for chiral HPLC analysis. The data given here is for the alcohol derivative*): Stationary phase = CHIRALPAK AS-H; Mobile Phase = 20:80 Isopropanol:Hexanes; Flow rate = 2 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

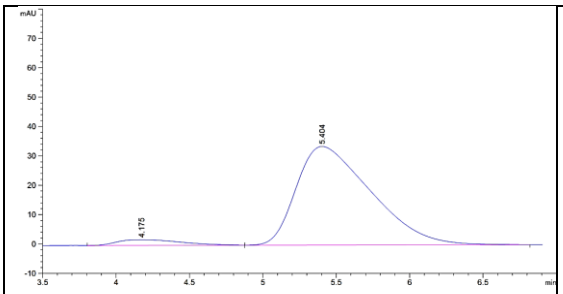
(a) Racemate of the alcohol derivative of **67**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.048	BV	0.3546	1481.53613	60.00051	50.8014
2	5.318	VB	0.4901	1434.79382	43.18307	49.1986

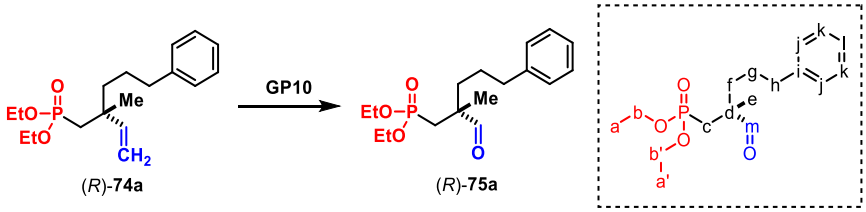
(b) R:S = 5:95, CAHB of (*E*/Z)-**18a** using (*R*)-**B2** followed by vinylation to obtain (*R*)-**67**. Hydroboration/oxidation of (*R*)-**67** is carried out to obtain the (*S*)-alcohol derivative.

Note: *The trace below is for the (S)-enriched alcohol derivative obtained from (R)-enriched* ***67****.*



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.175	BB	0.3620	57.41818	1.90327	4.6219
2	5.404	BB	0.5232	1184.89758	33.58085	95.3781

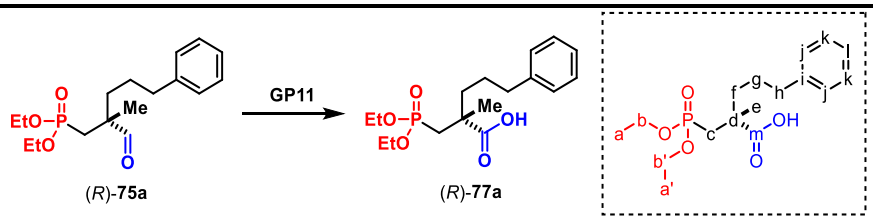
Representative procedure for the reductive ozonolysis of chiral vinyl phosphonates (GP10): The transformation was carried out according to the procedure[20] reported by Hon et. al. as follows: The chiral vinyl phosphonate (1 equiv.) is dissolved in CH_2Cl_2 (25 mL) ozone is bubbled through the reaction mixture for 10 minutes at 0 ^oC under air. Afterwards, triethylamine (5 equiv.) is added and the reaction mixture is stirred at room temperature for a total of 3 hours. The reaction mixture is concentrated under reduced pressure and is purified via flash chromatography on silica gel.



Ozonolysis of the vinylphosphonate (*R*)-**74a:** This transformation was carried out according to **GP10**. The vinylphosphonate (*R*)-**74a** (162 mg, 0.5 mmol, 1 equiv.) gives the phosphonoaldehyde (*R*)-**75a** (140 mg, 86%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 2:1) R_f = 0.5; $[\alpha]_D^{20}$ = +2.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.42 (1H, d, *J* = 1.2 Hz, m), 7.29-7.13 (5H, m, aryl), 4.11-4.02 (4H, m, b+b'), 2.62-2.57 (2H, m, h), 2.08-1.88 (2H, m, c), 1.77-1.46 (2H, m, f+g), 1.32-1.27 (6H, m, a+a'), 1.24 (3H, s, e); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.95 (d, $^3J_{C\text{-}P}$ = 9.75 Hz, m), 141.66 (i), 128.37 (aryl), 128.34 (aryl), 125.93 (aryl), 61.65-61.49 (m, b+b'), 46.88 (d, $^2J_{C\text{-}P}$ = 2.25 Hz, d), 36.14 (d, $^3J_{C\text{-}P}$ = 9 Hz, f), 36.08 (h), 30.93 (d, $^1J_{C\text{-}P}$ = 141 Hz, c), 25.84 (g), 20.03 (d, $^3J_{C\text{-}P}$ = 6 Hz, e), 16.43 (a+a'); ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.42 ppm; IR (neat) 3026.87 (sp^2 C-H), 2980.93 (sp^3 C-H), 2707.57 (aldehyde C-H), 1725.22 (C=O), 1236.37 (P=O) cm^{-1}; Enantiomer ratio = 98:2 (obtained for the derivative **79a**).

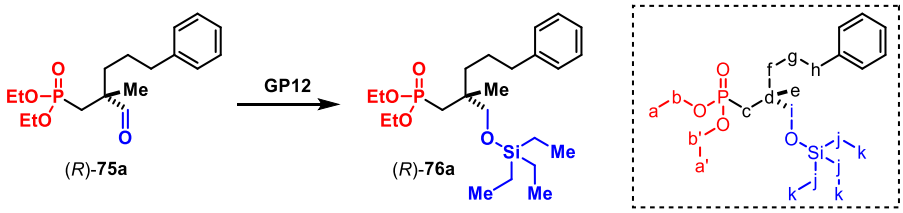
Representative procedure for the transformation of chiral vinylphosphonates into chiral phosphonate-functionalized carboxylic acids (GP11): The chiral vinyl phosphonate is subjected to ozonolysis according to **GP10**. Lindgren/Pinnick oxidation of the same was carried out according to the reported procedure[21] by Huang et. al. as follows: To a stirred solution of the chiral phosphonoaldehyde in *t*BuOH (2 mL/0.2 mmol) at room temperature, 2-methyl-2-butene (1.5 eq), aq. NaH_2PO_4 solution (0.50 *M*, 1.3 eq) and aq. $NaClO_2$ solution (0.50 *M*, 1.3 eq) are sequentially added. The reaction mixture is stirred

for a total of *ca.* 2 hours and then was quenched with the addition of aq. $NaHSO_3$ solution (1 mL/0.2 mmol phosphonoaldehyde, 1.0 M). The resulting mixture is extracted with ethyl-acetate and the combined extracts are washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Flash chromatography on silica gel is carried out to obtain the carboxylic acid.



Transformation of the vinylphosphonate (*R*)**-75a to chiral phosphonate-functionalized carboxylic acid** (*R*)**-77a:** This transformation is carried out according to **GP11**. The vinylphosphonate (*R*)-**75a** (64 mg, 0.2 mmol) yields the carboxylic acid (*R*)-**77a** (55 mg, 80%) as a colorless viscous oil: TLC analysis (ethyl acetate) $R_f = 0.5$; $[\alpha]_D^{20}$ = +5.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 10.25 (1H, br s, COOH), 7.25-7.11 (5H, m, aryl), 4.10-4.00 (4H, m, b+b'), 2.56 (2H, t, *J* = 6.6 Hz, h), 2.29-2.17 (1H, m, c), 1.98-1.87 (1H, m, c), 1.69-1.47 (4H, m, f+g), 1.28-1.25 (9H, m, a+a'+e) ppm; ^{13}C NMR (75 MHz, CD_2Cl_2) δ 178.39 (m), 142.23 (aryl), 128.33 (aryl), 128.23 (aryl), 125.72 (aryl), 62.08-61.85 (m, b+b'), 43.19 (d), 40.16 (d, $^3J_{C\text{-}P}$ = 14.25 Hz, f), 36.02 (f+h), 34.21 (d, $^1J_{C\text{-}P}$ = 138.75 Hz, c), 26.08 (g), 22.39 (d, $^3J_{C\text{-}P}$ = 6.75 Hz, e), 16.14 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, CD_2Cl_2) δ 28.88 ppm; IR (neat) 3025 (O-H), 2981 (sp^2 C-H), 2916 (sp^3 C-H), 1717 (C=O), 1453, 1166 (P=O), 1050 (C-O), 1021 (C-O), 961 (P-O) cm^{-1}; Enantiomer ratio = 98:2 (Obtained for the derivative **78a**).

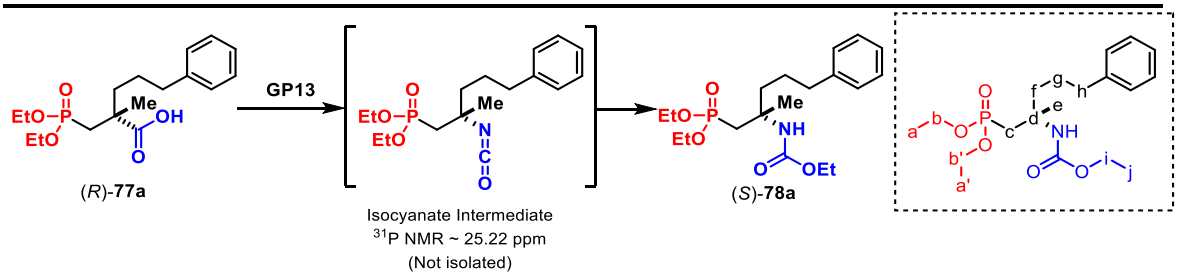
Representative procedure for the ruthenium-catalyzed reductive silylation of chiral phosphonoaldehydes (GP12): The synthesis of silyl protected chiral gamma amino phosphonate is carried out via reductive silylation of the chiral phosphonoaldehyde according to a reported procedure[22] by Gunanathan and co-workers as follows: To a stirred mixture of the chiral phosphonoaldehyde (1.0 eq) and [Ru(*p*-cymene)Cl_2]$_2$ (3.2 mol%) in toluene (0.5 mL/0.10 mmol phosphonoaldehyde) in a 4 mL vial was added triethylsilane (1.3 eq) and the resultant mixture is stirred at 50 ^oC for 9 hours. Afterwards the reaction mixture is concentrated and is purified using silica gel chromatography.



Transformation of phosphonoaldehyde (*R*)-75a to silyl-protected γ-hydroxy phosphonate (*R*)-76a: This transformation is carried out according to **GP12**. The phosphonoaldehyde (*R*)-**75a** (33 mg, 0.10 mmol, 1.0 equiv.) yields the silyl-protected γ-hydroxyphosphonate (*R*)-**76a** (32 mg, 72%) as a buff colored oil: TLC analysis (ethyl-acetate/hexanes 3:7) R_f = 0.5; $[\alpha]_D^{20}$ = –3.38^o (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.31-7.27 (2H, m, aryl), 7.21-7.17 (3H, m, aryl), 4.12-4.03 (4H, m, b+b'), 3.46-3.39 (2H, m, i), 2.60 (2H, t, *J* = 7.4 Hz, h), 1.83 (2H, d, *J* = 19.2 Hz, c), 1.64-1.46 (4H, m, f+g), 1.33 (6H, t, *J* = 7.1 Hz, a+a'), 1.04 (3H, s, e), 0.97 (9H, t, *J* = 8.0 Hz, k), 0.60 (6H, q, *J* = 8.0 Hz, j) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) δ 142.93 (aryl), 128.57 (aryl), 128.44 (aryl), 125.83 (aryl), 69.48 (d, $^3J_{C\text{-}P}$ = 12 Hz, i), 61.21 (d, $^2J_{C\text{-}P}$ = 7 Hz, b+b'), 37.60 (d, $^3J_{C\text{-}P}$ = 7 Hz, f), 37.58 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 36.93 (h), 32.55 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 26.11 (g), 22.63 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, e), 16.65 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a'), 7.02 (k), 4.59 (j) ppm; ^{31}P NMR (162 MHz,

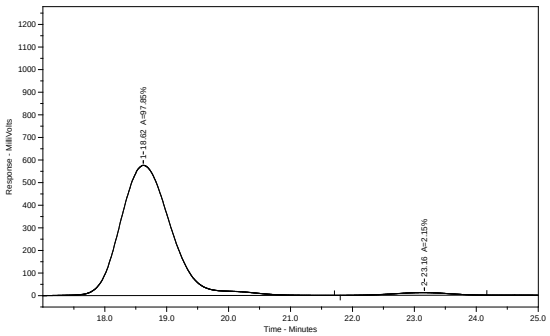
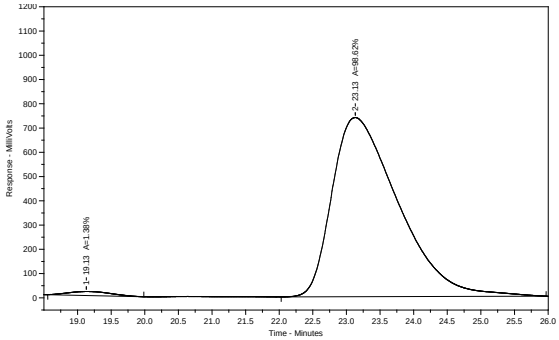
CD_2Cl_2) δ 31.24 ppm; IR (neat) 2952 (aromatic C-H), 2875 (aliphatic C-H), 1242 (P=O & Si-C), 1088 (C-O & Si-OR), 1055 (C-O & Si-OR), 1026 (Si-OR & P-OR), 954 (P-O) cm^{-1}.

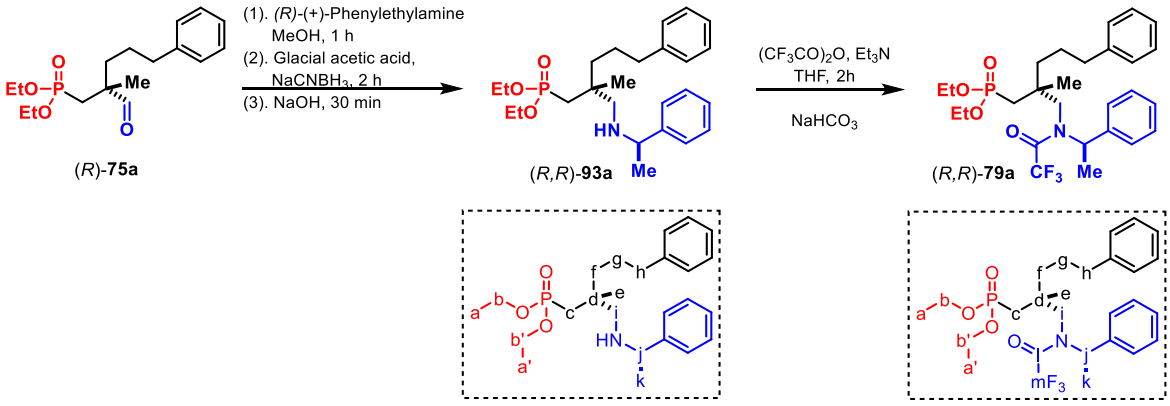
Representative procedure for the synthesis of chiral β-amino phosphonates via Curtius rearrangement (GP13): The transformation is carried out with slight modifications of the reported procedure[23] by Sigman et. al. as follows: To a stirred mixture of the quaternary phosphono-carboxylic acid (1 eq) and triethylamine (3 eq) in dry toluene (1 mL/0.1 mmol phosphono-carboxylic acid), diphenyl phosphoryl azide (1.4 eq) is added dropwise at room temperature and the resultant mixture heated to reflux for 3 hours. ^{31}P NMR analysis shows the disappearance of the starting material peak and a new field upfield relative to the starting material corresponding to the isocyanate intermediate. To the resultant mixture, dry ethanol (0.3 mL/0.1 mmol phosphono-carboxylic acid) is added and the resultant mixture refluxed for 6 hours. Afterwards, the reaction mixture is concentrated, and the product purified via flash chromatography on silica gel.



Synthesis of chiral β-aminophosphonate (*S*)-**78a:** This transformation was carried out according to GP13. The phosphono-carboxylic acid (*R*)-**77a** (35 mg, 0.1 mmol, 1.0 equiv.) was transformed to chiral β-aminophosphonate (*S*)-**78a** (29 mg, 76%), the latter was formed as a colorless oil: TLC analysis (ethyl-acetate/hexanes 1:1) $R_f = 0.5$; $[\alpha]_D^{20} = +3.75^o$

(*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, CD_2Cl_2) δ 7.31-7.17 (5H, m, aryl), 5.21 (1H, br s, NH), 4.12-4.02 (6H, m, b+b'+i), 2.62 (2H, t, *J* = 7.8 Hz, h), 2.41-2.30 (1H, m, c), 2.18-2.06 (1H, m, c), 2.04-1.77 (2H, m, f), 1.67-1.56 (2H, m, g), 1.44 (3H, s, e), 1.31 (6H, t, *J* = 7.1 Hz, a+a'), 1.23 (3H, t, *J* = 7.2 Hz, j) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.14 (carbamate carbonyl carbon), 142.29 (aryl), 128.35 (aryl), 128.32 (aryl), 125.80 (aryl), 61.46 (d, $^2J_{C-P}$ = 6 Hz, b+b'), 60.19 (i), 53.27 (d, $^2J_{C-P}$ = 3.75 Hz, d), 39.91 (d, $^3J_{C-P}$ = 10.5 Hz, f), 36.00 (h), 34.65 (d, $^1J_{C-P}$ = 136.5 Hz, c), 25.89 (g), 25.71 (d, $^3J_{C-P}$ = 7.5 Hz, e), 16.38 (d, $^3J_{C-P}$ = 6 Hz, a+a'), 14.58 (j) ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.04 ppm; IR (neat) 3292 (N-H), 3026 (aromatic C-H), 2935 (aliphatic C-H), 1713 (C=O), 1388 (C-N), 1229 (P=O), 1051 (C-O), 1024 (C-O), 957 (P-O) cm^{-1}; Enantiomer ratio = 98:2, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 100% Isopropanol; Flow rate = 1 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a). R:S = 2:98, Curtius rearrangement of (*R*)-**78a**:	(b). R:S = 98:2, Curtius rearrangement of (*S*)-**78a**:
	

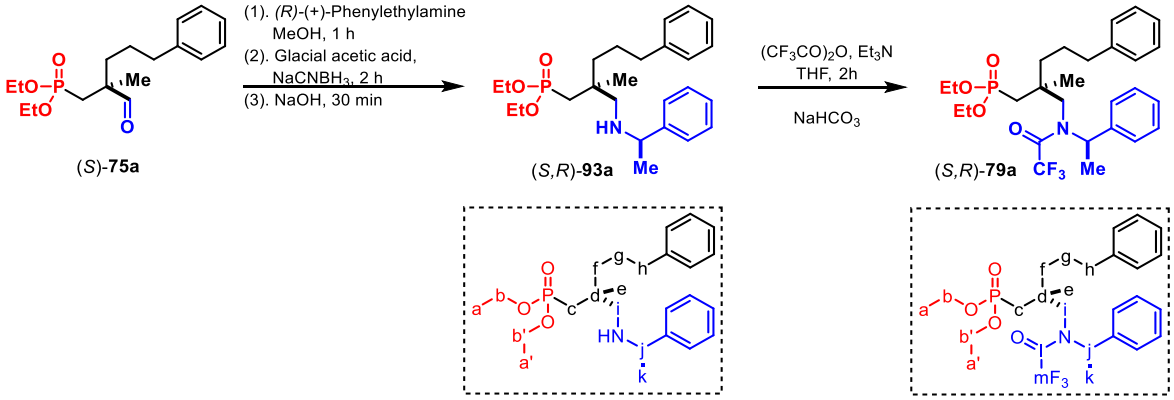


Representative procedure for the synthesis of chiral γ-amino phosphonate via tandem reductive amination and trifluoroacetylation (GP14) A mixture of the quaternary chiral aldehyde (*R*)-**75a** (65 mg, 0.20 mmol, 1.0 eq) and (*R*)-(+)-Phenylethylamine (26 mg, 0.20 mmol, 1.0 eq) in methanol (1 mL) was stirred at room temperature for 1 hour. [*Note: This premixing affords cleaner reductive amination products presumably due to quantitative imine formation in methanol as described by Magid et. al*[24]*. Reductive aminations carried out without premixing in methanol are usually contaminated with product arising from the reduction of the aldehyde*.] Glacial acetic acid (30 μL, 2.6 eq) is added to the mixture followed by sodium cyanoborohydride (13 mg, 1.0 eq) and the resultant mixture is stirred at room temperature for 2 hours. The reaction is quenched with the addition of 1 mL of 20% aqueous NaOH and the resultant mixture stirred for 30 minutes. Afterwards, the product is extracted with CH_2Cl_2 (10 mL x 3) and the combined extracts are dried over anhydrous magnesium sulfate and concentrated in vacuum. Flash chromatography on silica gel (methanol/ethyl-acetate 1:50) affords the gamma amino phosphonate (*R*,*R*)-**93a** as a colorless oil (70 mg, 81%): TLC analysis (methanol/ethyl-acetate 1:50) R_f = 0.5; $[\alpha]_D^{20}$ = +17.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.18 (10H, m, aryl), 4.09-4.03 (4H, m, b+b'), 3.68 (1H, q, *J* = 6.8 Hz, j), 2.60-2.57 (2H, m, h), 2.49 (1H, d, *J* = 12 Hz, i), 2.26 (1H, d, *J* = 12 Hz, i), 1.91-1.73 (2H, m, c), 1.56-1.44 (5H, m, f+g+NH), 1.34-1.29

(9H, m, a+a'+k), 1.03 (3H, s, e) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.59 (aryl), 142.85 (aryl), 128.58 (aryl), 128.45 (aryl), 128.43 (aryl), 126.83 (aryl), 125.87 (aryl), 61.25 (dd, $^2J_{C\text{-}P}$ = 6 Hz, b+b'), 59.05 (j), 56.44 (d, $^3J_{C\text{-}P}$ = 10 Hz, i), 38.68 (d, $^3J_{C\text{-}P}$ = 8 Hz, f), 36.74 (h), 36.40 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 33.83 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 25.89 (g), 24.89 (k), 24.62 (d, $^3J_{C\text{-}P}$ = 9 Hz, e), 16.65 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.19 ppm; IR (neat) 3308 (N-H), 3061 (aromatic C-H), 2978 (aliphatic C-H), 1603 (N-H), 1494 (aromatic C=C), 1452 (aromatic C=C), 1233 (P=O), 1054 (C-O), 1025 (C-O), 955, 748, 698 cm^{-1}. Diastereomer ratio (dr) = 98:2 (determined from the ^{1}H and ^{31}P NMR analysis of the acylated derivative (*R*,*R*)-**79a**).

Preparation of (*R*,*R*)-**79a:** Trifluoroacetic anhydride (30 µL, 0.21 mmol, 2.1 eq) is added to a mixture of (*R*,*R*)-**93a** (44 mg, 0.10 mmol, 1.0 eq) and triethylamine (70 µL, 0.50 mmol, 5.0 eq) in dry THF (0.5 mL) and the resultant mixture is stirred at room temperature for 2 hours. Afterwards, saturated $NaHCO_3$ is added (0.5 mL) and the reaction mixture extracted with ethyl-acetate (5 mL x 3). The combined organics are washed with brine, concentrated in vacuum and purified by flash chromatography on silica gel (ethyl-acetate/hexanes 3:7) to afford the product (*R*,*R*)-**79a** (49.5 mg, 94%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 3:7) R_f = 0.5; $[\alpha]_D^{20}$ = +10.2^o (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.15 (10H, m, aryl), 5.31 (1H, q, *J* = 6.8 Hz, j), 4.05-3.93 (4H, m, b+b'), 3.43 (1H, d, *J* = 14.4 Hz, i), 3.26 (1H, d, *J* = 14.8 Hz, i), 2.53 (2H, broad m, h), 1.66-1.24 (15H, m, a+a'+c+f+g+k), 0.79 (2.93H, s, e; Major diastereomer), 0.74 (0.07H, s, e; Minor diastereomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.70 (d, $^2J_{C\text{-}F}$ = 35 Hz, l), 142.70 (aryl), 138.54 (aryl), 129.05 (aryl), 128.69 (aryl), 128.59 (aryl), 128.50 (aryl), 128.28

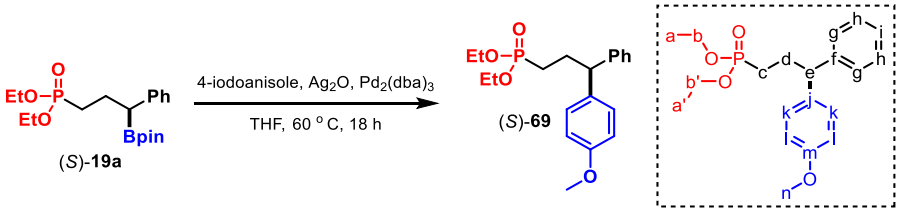
(aryl), 125.96 (aryl), 61.30 (dd, $^{2}J_{C\text{-}P}$ = 4.0 Hz, b+b'), 56.04 (j), 52.83 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, i), 40.13 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, f), 36.82 (d, $^{2}J_{C\text{-}P}$ = 3 Hz, d), 36.63 (h), 34.76 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 26.33 (g), 24.76 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, e), 18.31 (k), 16.61 (dd, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.09 (Minor diastereomer, 2%), 29.93 (Major diastereomer, 98%) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.41 ppm; IR (neat) 2981 (aromatic C-H), 2937 (aliphatic C-H), 1687 (C=O), 1496, 1453, 1389, 1199 (P=O), 1136, 1097, 1053, 1025, 955 cm^{-1}.



Synthesis of diastereomeric γ-aminophosphonate (*S*,*R*)-**79a:** (*S*)-**75a** (65 mg, 0.20 mmol, 1.0 eq) was subjected to reductive amination as per the protocol outlined in **GP14**. Flash chromatography on silica gel afforded the diastereomeric gamma amino phosphonate (*S*,*R*)-**93a** as a colorless oil (72 mg, 83%): TLC analysis (methanol/ethyl-acetate 1:50) R_f = 0.5; $[\alpha]_D^{20}$ = +12.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.16 (10H, m, aryl), 4.12-4.04 (4H, m, b+b'), 3.68 (1H, q, *J* = 6.8 Hz, j), 2.59-2.55 (2H, m, h), 2.47 (1H, d, *J* = 12 Hz, i), 2.28 (1H, d, *J* = 12 Hz, i), 1.95-1.71 (2H, m, c), 1.51-1.42 (5H, m, f+g+NH), 1.35-1.30 (9H, m, a+a'+k), 1.03 (3H, s, e) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.59 (aryl), 142.83 (aryl), 128.56 (aryl), 128.41 (aryl), 126.84 (aryl), 125.85 (aryl), 61.25 (d, $^{2}J_{C\text{-}P}$ = 7 Hz, b+b'), 59.07 (j), 56.18 (d, $^{3}J_{C\text{-}P}$ = 9 Hz, i), 39.18 (d, $^{3}J_{C\text{-}P}$ = 11 Hz, f), 36.70 (h), 36.34 (d, $^{2}J_{C\text{-}P}$ = 3 Hz, d), 34.03 (d, $^{1}J_{C\text{-}P}$ = 136 Hz, c), 25.79 (g), 24.94 (k), 24.26 (d,

$^{3}J_{C\text{-}P}$ = 7 Hz, e), 16.64 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.21 ppm; IR (neat) 3308 (N-H), 3061 (aromatic C-H), 2978 (aliphatic C-H), 1603 (N-H), 1494 (aromatic C=C), 1452 (aromatic C=C), 1233 (P=O), 1054 (C-O), 1025 (C-O), 955, 748, 698 cm^{-1}. Diastereomer ratio (dr) = 98:2 (determined from the ^{1}H and ^{31}P NMR analysis of the derivative (*S,R)*-**79a**).

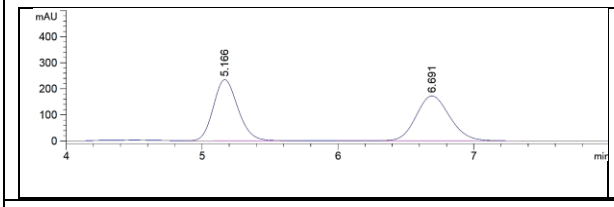
Preparation of (*S,R*)-**79a:** Similar to the procedure outlined for the preparation of (*R,R*)-**79a**, (*S,R*)-**93a** (30 mg, 70 µmol, 1.0 eq) yields (*S,R*)-**79a** (37 mg, 91%) as a colorless oil: TLC analysis (etyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = +12.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.13 (10H, m, aryl), 5.31 (1H, q, *J* = 6.8 Hz, j), 4.08-3.97 (4H, m, b+b'), 3.52 (1H, d, *J* = 14.4 Hz, i), 3.24 (1H, d, *J* = 14.8 Hz, i), 2.43 (2H, broad m, h), 1.96-1.12 (15H, m, a+a'+c+f+g+k), 0.80 (0.06H, s, e; Minor diastereomer), 0.74 (2.94H, s, e; Major diastereomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.07 (d, $^{2}J_{C\text{-}F}$ = 35 Hz, l), 142.77 (aryl), 138.42 (aryl), 129.97 (aryl), 128.74 (aryl), 128.57 (aryl), 128.51 (aryl), 128.48 (aryl), 125.93 (aryl), 61.34 (dd, $^{2}J_{C\text{-}P}$ = 4.0 Hz, b+b'), 56.22 (j), 52.31 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, i), 39.96 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, f), 36.92 (d), 36.62 (h), 35.16 (d, $^{1}J_{C\text{-}P}$ = 137 Hz, c), 26.22 (g), 24.71 (d, $^{3}J_{C\text{-}P}$ = 10 Hz, e), 18.29 (k), 16.61 (dd, $^{3}J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.05 (Major diastereomer, 98%), 29.90 (Major diastereomer, 2%) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.42 ppm; IR (neat) 2980 (aromatic C-H), 2935 (aliphatic C-H), 1690 (C=O), 1496, 1452, 1389, 1197 (P=O), 1138, 1097, 1057, 1025, 956 cm^{-1}.



General procedure for palladium-catalyzed cross coupling of chiral secondary benzylic boronic esters with 4-iodoanisole (GP15): This transformation is carried out with slight modifications of the original procedure[25] reported by Crudden and co-workers as follows. The chiral secondary benzylic boronic ester (*S*)-**19a** (102 mg of 88% purity containing 90.0 mg of (*S*)-**19a**, 0.23 mmol, 1.00 equiv), 4-iodoanisole (73.0 mg, 0.31 mmol, 1.35 equiv), Ag_2O (72.6 mg, 0.31 mmol, 1.35 equiv), PPh_3 (84.0 mg, 0.32 mmol) and $Pd_2(dba)_3$ (11.4 mg, 12.4 μmol, 10.7 mol% Pd) are taken up in dry THF (4 mL) in an oven dry 8 mL vial charged with borosilicate glass beads. The vial is sealed inside the glovebox, taken outside and is vigorously shaken for 18 hours in a shaker-incubator at 60 ^oC for 18 hours. Afterwards, the reaction mixture is filtered, and the concentrated filtrate is purified via silica gel chromatography (ethyl acetate/hexanes 3:1) to afford the desired cross-coupled product (*S*)-**69** (50 mg, 60%) as a colorless oil (**Note:** *In this procedure, triphenylphosphine oxide is a major side product and it overlaps significantly with the cross-coupling product (S)-**69**. Separating (S)-**69** from triphenylphosphine oxide and the protodeborylated side product isn't trivial and traces of triphenylphosphine oxide peaks can be seen in the NMR's of (S)-**69**.*): TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.4; $[\alpha]_D^{20}$ = +6.5^o (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30-7.28 (2H, m, h), 7.23 (2H, d, *J* = 7.25 Hz, g), 7.20-7.18 (1H, t, *J* = 7.25 Hz, i), 7.16 (2H, d, *J* = 8.65 Hz, k), 6.85 (2H, d, *J* = 8.65 Hz, l), 4.12-4.03 (4H, m, b+b'), 3.90 (1H, t, *J* = 7.9 Hz, e), 3.78 (3H, s, n), 2.36-2.29 (2H, m, d), 1.75-1.65 (2H, m, c), 1.31 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.26 (m), 144.37 (f), 136.07 (j), 128.90 (k),128.71 (g), 127.87 (h), 126.49 (i), 144.10 (l), 61.63 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 55.36 (n), 51.11 (d, $^3J_{C\text{-}P}$ = 18 Hz, e), 28.56 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, d), 24.50 (d, $^1J_{C\text{-}P}$ = 141 Hz, c), 16.62 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a')

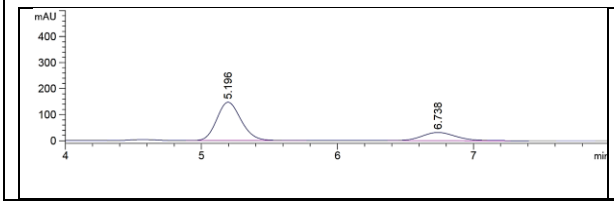
ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.11 ppm; IR (neat) 2985 (C-H), 1458 (aromatic C=C), 1247 (P=O), 1025 (C-O), 959 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{20}H_{27}O_4P+Na^+$ = 385.1545. found 385.1554 *m/z*. Enantiomer ratio = 77:23, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 40:60 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate



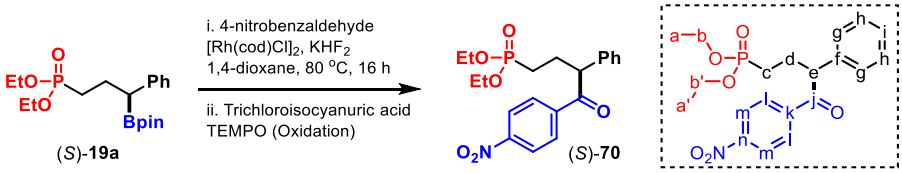
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.166	VB	0.1944	2938.63208	49.9252
2	6.691	BB	0.2658	2947.43970	50.0748

(b) R:S = 23:77, CAHB of (*E*/Z)-**18a** using (*R*)-**B2** followed by cross-coupling with 4-iodoanisole to form **69**.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.196	VB	0.1922	1834.83081	77.4636
2	6.738	BB	0.2643	533.80627	22.5364

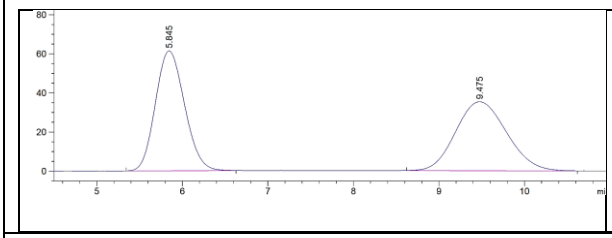
Absolute configuration assignment: The chiral boronic ester (*S*)-**19a** (102 mg of 88% purity containing 90.0 mg of (*S*)-**19a**, 0.23 mmol, 1.00 equiv) is subjected to cross-coupling under Crudden's Conditions (**GP15**) with 2-iodobenzofuran (76.0 mg, 0.31 mmol, 1.35 equiv) to afford (*S*)-**68** (47 mg, 55%; 71:29 er). Matching the HPLC traces of **68** formed from (*S*)-**19a** with **GP8** and **GP15** (see HPLC traces under **GP8**) shows that **68** is formed with predominant retention of stereochemistry using **GP15**. Hence, **GP15** with (*S*)-**19a** occurs with retention of stereochemistry and the configuration of (*S*)-**69** is assigned based on this analogy.



General procedure for rhodium-catalyzed cross-coupling of chiral secondary benzylic boronic esters with 4-nitrobenzaldehyde/oxidation (GP16): The first step of coupling is carried out according to Tang's modification[26] of the original procedure[27] reported by Aggarwal and co-workers as follows. The chiral secondary benzylic boronic ester (*S*)-**19a** (108 mg of 88% purity containing 95.0 mg of (*S*)-**19a**, 0.25 mmol, 1.00 equiv), 4-nitrobenzaldehyde (50.0 mg, 0.33 mmol, 1.32 equiv) and $[Rh(cod)Cl]_2$ (5.0 mg, 10 μmol, 4 mol%) are taken up in deoxygenated dioxane (2.5 mL) in an oven dry 8 mL vial charged with a stir-bar inside the glovebox. The resultant mixture is stirred vigorously for 10 minutes. Following this, a solution of KHF_2 in deoxygenated H_2O (80 mg KHF_2 dissolved in 1 mL H_2O; 0.35 mL, 0.36 mmol, 1.43 eq) is added drop-wise to the above solution and the resultant mixture is sealed, taken outside the glovebox and is stirred vigorously at 80 ^oC for 16 hours. Afterwards, the reaction mixture is cooled down to room temperature and saturated aqueous NH_4Cl solution (2 mL) is added and the mixture is extracted with ethyl acetate (3 mL x 5). The combined organics are washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Flash chromatography over silica gel (1% methanol in ethyl acetate) affords the alcohol product as a sticky liquid (84 mg, 82%) as a mixture of diastereomers. To a cooled (0 ^oC) solution of the diastereomeric alcohols (84 mg, 0.2 mmol) and trichloroisocyanuric acid (47 mg, 0.2 mmol) in dichloromethane (1.0 mL), TEMPO (6 mg, 20 mol%) is added and the resultant mixture is stirred at room temperature for 2 hours. Afterwards, the reaction mixture is diluted with dichloromethane, washed with water and brine and dried over anhydrous Na_2SO_4. Flash chromatography over silica gel

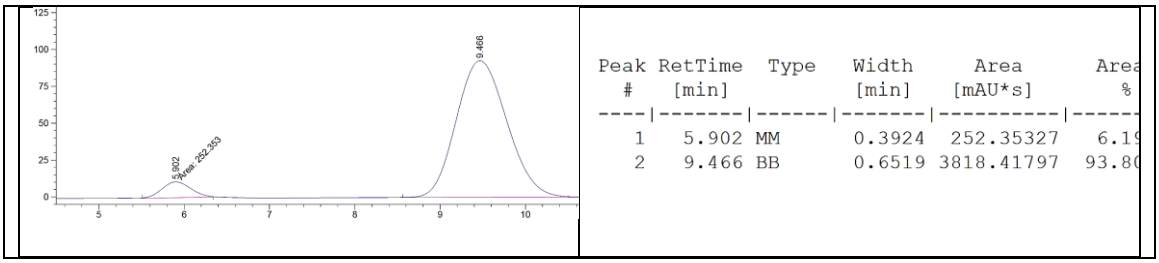
(ethyl acetate) affords the ketone product (*S*)-**70** as a sticky liquid (75 mg, 74% yield over 2 steps): TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +78° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (2H, d, *J* = 9.0 Hz, l or m), 8.09 (2H, d, *J* = 9.0 Hz, l or m), 7.41-7.21 (5H, m, g+h+i), 4.78 (1H, t, *J* = 7.25 Hz, e), 4.17-4.03 (4H, m, b+b'), 2.56-2.40 (1H, m, d(1H)), 2.22-2.10 (1H, m, d(1H)), 1.86-1.65 (2H, m, c), 1.32 (3H, t, *J* = 7.0 Hz, a or a'), 1.31 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.92 (j), 150.24 (n), 141.29 (k), 137.80 (f), 129.92 (l), 129.63 (g or h), 128.49 (g or h), 128.04 (i), 123.93 (m), 61.85 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.81 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 54.19 (d, $^3J_{C\text{-}P}$ = 12.5 Hz, e), 26.68 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 23.31 (d, $^1J_{C\text{-}P}$ = 141 Hz, c), 16.66 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.26 ppm; IR (neat) 2981 (C-H), 1687 (C=O), 1524 (N-O), 1344 (N-O), 1223 (P=O), 1052 (C-O), 1022 (C-O), 946 (P-O), 700 cm^{-1}; HRMS (ESI) calculated for $C_{20}H_{24}NO_6P$+Na^+ = 428.1239, found 428.1241 *m/z*. Enantiomer ratio = 6:94, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 75:25 Isopropanol:Hexanes; Flow rate = 1.5 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate

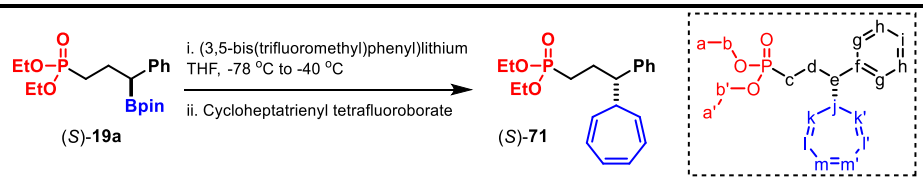


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.845	BB	0.3725	1454.32874	49.9927
2	9.475	BB	0.6524	1454.75562	50.0073

(b) R:S = 6:94, CAHB of (*E*/Z)-**18a** using (*R*)-**B2** followed by cross-coupling with 4-nitrobenzaldehyde, followed by oxidation to yield (*S*)-**70**:



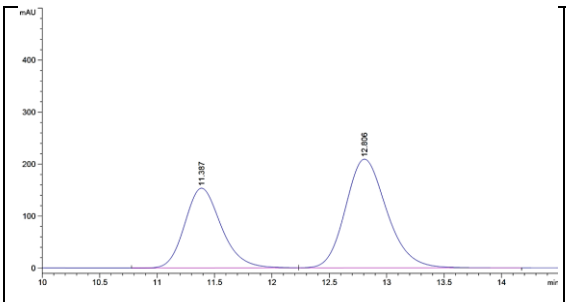
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.902	MM	0.3924	252.35327	6.19
2	9.466	BB	0.6519	3818.41797	93.80



General procedure for S_E2 reaction of boron-ate complexes of chiral secondary benzylic boronic esters with electrophiles (GP17): This transformation is carried out with slight modifications of the original protocol[28] developed by Aggarwal and co-workers as follows. To a solution of 3,5-bis(trifluoromethyl)bromobenzene (89 mg, 0.3 mmol, 1.5 equiv) in dry THF (3 mL) at -78 °C is added *n*BuLi in hexanes (2.5M solution; 0.12 mL, 0.3 mmol, 1.5 equiv) dropwise. The resultant solution is stirred for 1 hour at -78 °C. A solution of (*S*)-**19a** (86 mg of 88% purity containing 76 mg (*S*)-**19a**, 0.2 mmol, 1.0 equiv) in dry THF (1 mL) is added drop-wise to the solution of (3,5-bis(trifluoromethyl)phenyl)lithium at -78 °C. The resultant mixture is stirred for 30 minutes in the dry ice-acetone bath (-78 °C). Following this, the dry ice-acetone bath is replaced by a dry ice-acetonitrile bath (-40 °C) and the resultant mixture stirred for another 30 minutes. At this point, solid cycloheptatrienyl tetrafluoroborate (71 mg, 0.4 mmol, 2.0 equiv) is added to the reaction mixture at room temperature and the reaction mixture stirred vigorously for 1 hour. A saturated aqueous solution of $NaHCO_3$ is added and the reaction mixture is extracted with ethyl acetate (20 mL x 3). The combined organics are washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash

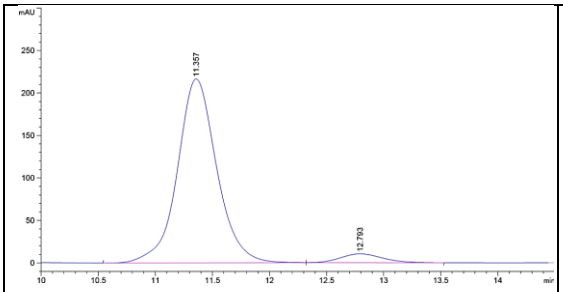
chromatography over silica gel (4:1 ethyl acetate/hexanes) affords the desired product (*S*)-**71** (66 mg, 95%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.6; $[\alpha]_D^{20}$ = -64º (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.30 (2H, m, aryl), 7.25-7.21 (1H, m, aryl), 7.14-7.12 (2H, m, aryl), 6.72-6.23 (2H, m, m+m'), 6.28 (1H, dd, *J* = 9.5, 5.5 Hz, l or l'), 6.03 (1H, dd, *J* = 9.5, 5.5 Hz, l or l'), 5.39 (1H, dd, *J* = 9.5, 6.0 Hz, k or k'), 4.98 (1H, dd, *J* = 9.5, 6.0 Hz, k or k'), 4.12-3.96 (4H, m, b+b'), 2.90 (1H, td, *J* = 11, 3.5 Hz, e), 2.40-2.30 (1H, m, d(1H)), 1.86-1.73 (2H, m, d(1H)+j), 1.63-1.45 (2H, m, c), 1.29 (3H, t, *J* = 7.0 Hz, a or a'), 1.28 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.59 (f), 131.11 (m or m'), 130.82 (m or m'), 128.76 (aryl), 128.56 (aryl), 126.89 (aryl), 125.30 (l or l'), 124.81 (k or k'), 124.63 (k or k'), 124.42 (l or l'), 61.56 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 48.80 (d, $^3J_{C\text{-}P}$ = 16.5 Hz, e), 44.55 (j), 27.63 (d, $^2J_{C\text{-}P}$ = 4.5 Hz, d), 23.50 (d, $^1J_{C\text{-}P}$ = 141 Hz, c), 16.57 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.30 ppm; IR (neat) 2981 (C-H), 1584 (C=C), 1494 (aromatic C=C), 1453 (aromatic C=C), 1391 (aromatic C=C), 1237 (P=O), 1054 (C-O), 1022 (C-O), 959 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{20}H_{27}O_3P+Na^+$ = 369.1596, found 369.1595 *m/z*. Enantiomer ratio = 95:5, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 10:90 Isopropanol:Hexanes; Flow rate = 1.0 mL/min; HPLC UV Detector λ = 210 nm, 25 ºC. HPLC traces:

(a) Racemate

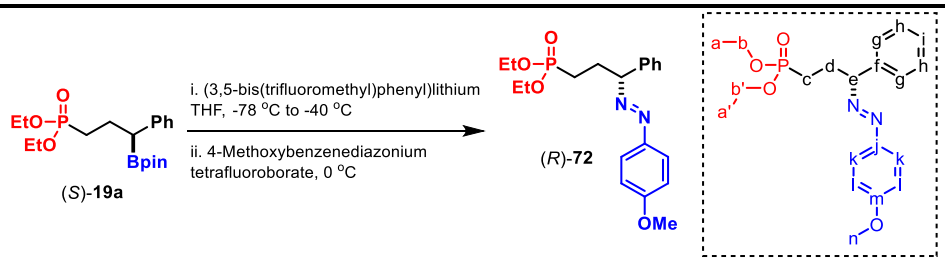


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.387	BV	0.3407	3401.77856	153.40106	39.3958
2	12.806	VB	0.3855	5233.10303	209.06151	60.6042

(b) R:S = 95:5, CAHB of (*E*/Z)-**18a** using (*R*)-**B2** followed by S_E2 to form (*S*)-**71**:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.357	BB	0.3613	5162.74805	216.40097	95.2596
2	12.793	BB	0.3845	256.91110	10.28351	4.7404

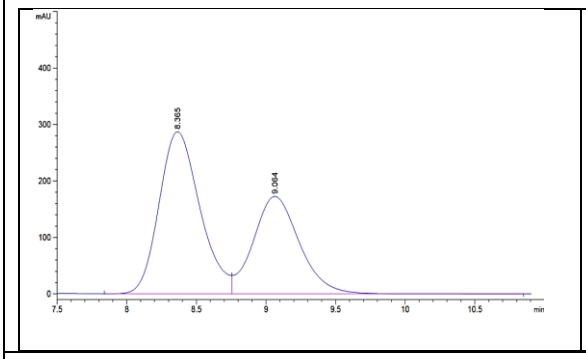


S_E2 reaction with 4-methoxybenzenediazonium tetrafluoroborate: This transformation is carried according to **GP17** with few changes as follows. To a solution of 3,5-bis(trifluoromethyl)bromobenzene (89 mg, 0.3 mmol, 1.5 equiv) in dry THF (3 mL) at -78 °C is added *n*BuLi in hexanes (2.5M solution; 0.12 mL, 0.3 mmol, 1.5 equiv) dropwise. The resultant solution is stirred for 1 hour at -78 °C. A solution of (*S*)-**19a** (86 mg of 88% purity containing 76 mg (*S*)-**19a**, 0.2 mmol, 1.0 equiv) in dry THF (1 mL) is added drop-wise to the solution of (3,5-bis(trifluoromethyl)phenyl)lithium at -78 °C. The resultant mixture is stirred for 30 minutes in the dry ice-acetone bath (-78 °C). Following this, the dry ice-acetone bath is replaced by a dry ice-acetonitrile bath (-40 °C) and the resultant mixture stirred for another 30 minutes. Afterwards the dry ice-acetonitrile bath is removed, and the reaction flask is covered with an aluminum foil and placed in an ice-bath. The lights inside the fume hood are turned off and solid 4-methoxybenzenediazonium tetrafluoroborate (89 mg, 0.4 mmol, 2.0 equiv) is added directly to the reaction mixture

under vigorous stirring. The reaction mixture is stirred for 5 minutes at 0°C and is allowed to warm up to room temperature over 30 minutes. A saturated aqueous solution of $NaHCO_3$ is added and the reaction mixture is extracted with ethyl acetate (20 mL x 3). The combined organics are washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure in the rotovap (water bath temperature set at 35 °C). Flash chromatography over silica gel (4:1 ethyl acetate/hexanes) affords the desired product (*R*)-**72** (43 mg, 55%) as a bright orange liquid (**Note:** *The diazo product (R)-**72** is highly light and heat sensitive. Care is taken to rigorously exclude light from the point the electrophile is added to the reaction mixture and through all work-up and purification procedures. The temperature of the water bath in rotovap is kept at 35 °C to concentrate the product. The product decomposed in chloroform within minutes, however, it is found to be stable in dichloromethane, methanol and isopropanol. NMR data for this compound is hence recorded using deuterated dichloromethane.*): TLC analysis (ethyl acetate) $R_f = 0.4$; $[\alpha]_D^{20}$ = -9.75° (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 (2H, d, *J* = 9.0 Hz, k), 7.51 (2H, d, *J* = 7.3 Hz, g), 7.42 (2H, dd, *J* = 7.7, 7.3 Hz, h), 7.34 (1H, t, *J* = 7.3 Hz, i), 6.99 (2H, d, *J* = 9.0 Hz, l), 4.71 (1H, t, *J* = 7.1 Hz, e), 4.13-4.01 (4H, m, b+b'), 3.88 (3H, s, n), 2.54-2.33 (2H, m, d), 1.78-1.62 (2H, m, c), 1.31 (6H, t, *J* = 7.0 Hz, a+a') ppm; ^{13}C NMR (175 MHz, CD_2Cl_2) δ 161.86 (m), 146.07 (j), 140.12 (f), 128.64 (h), 127.88 (g), 127.64 (i), 124.19 (k), 113.95 (l), 81.85 (d, $^3J_{C\text{-}P}$ = 17 Hz, e), 61.49 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 55.53 (n), 28.44 (d, $^2J_{C\text{-}P}$ = 3.5 Hz, d), 22.38 (d, $^1J_{C\text{-}P}$ = 141.5 Hz, c), 16.25 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, CH_2Cl_2) δ 30.96 ppm; IR (neat) 2981 (aromatic C-H), 2832 (aliphatic C-H), 1506 (N=N stretch), 1441 (aromatic C=C), 1391 (aromatic C=C), 1230 (P=O), 1141 (C-N), 1023 (C-O), 959 (P-O) cm^{-1}; HRMS (ESI) calculated for

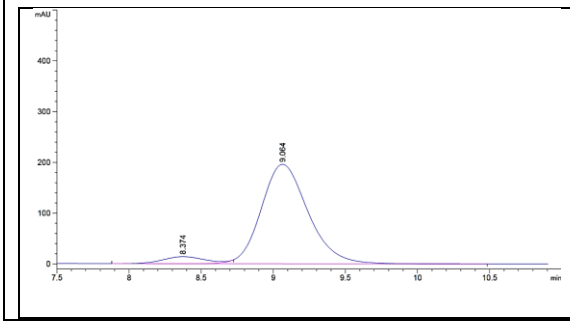
$C_{20}H_{27}N_2O_4P+Na^+$ = 413.1606, found 413.1602 *m/z*. Enantiomer ratio = 95:5, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 30:70 Isopropanol:Hexanes; Flow rate = 1.0 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) Racemate



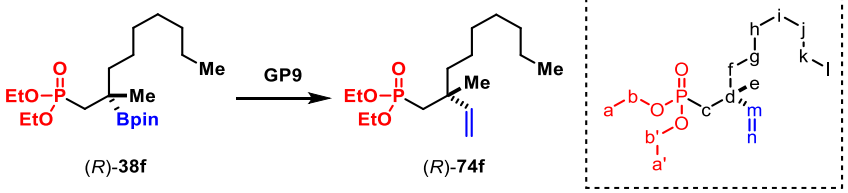
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.365	BV	0.3134	5843.08154	287.09207	59.5381
2	9.064	VB	0.3505	3970.94214	172.56721	40.4619

(b) R:S = 95:5, CAHB of (*E*/Z)-**18a** using (*R*)-**B2** followed by S_E2 to form (*R*)-**72**:



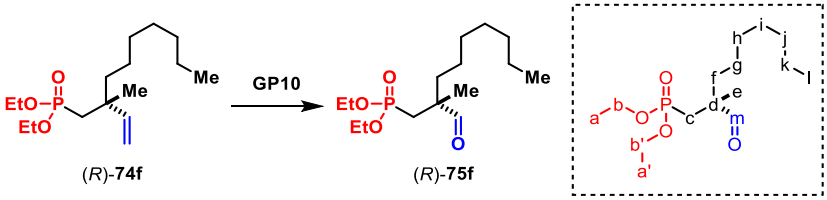
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.374	BV E	0.3090	274.26266	13.88309	5.8206
2	9.064	VB R	0.3476	4437.70410	196.00299	94.1794

5.8. Miscellaneous transformations of phosphonate-functionalized chiral tertiary boronic esters without chromophores to determine enantiomer ratios



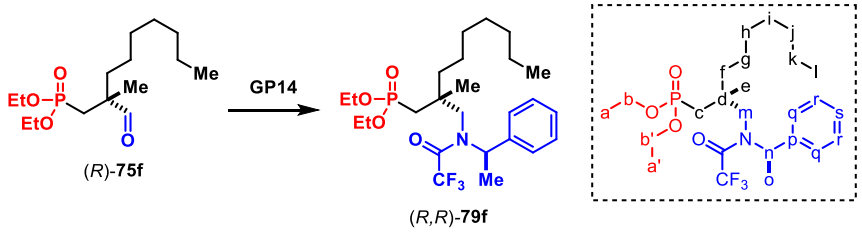
Synthesis of chiral vinyl phosphonate (*R*)-**74f:** Following the general procedure for vinylation of chiral tertiary boronic esters (**GP9)**, the chiral tertiary boronic ester (*R*)-**38f**

(81 mg, 0.20 mmol) yields the chiral vinyl phosphonate (*R*)-**74f** (56 mg, 91%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = –0.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, dd, *J* = 17.2, 10.8 Hz, m), 5.03-4.94 (2H, m, n), 4.14-4.00 (4H, m, b+b'), 1.85 (2H, d, *J* = 18.8 Hz, c), 1.53-1.21 (21H, m, a+a'+e+f+g+h+i+j+k) 0.88 (3H, t, *J* = 6.8 Hz, l) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.59 (d, $^3J_{C\text{-}P}$ = 10 Hz, m), 111.57 (n), 61.31-61.13 (m, b+b'), 41.90 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 38.28 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 36.85 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 31.99, 30.28, 29.42, 24.29, 24.14 (d, $^3J_{C\text{-}P}$ = 6 Hz, e), 22.76 (g), 16.52 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a'), 14.19 (l) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.86 ppm; IR (neat) 2956 (sp^2 C-H), 2856 (sp^3 C-H), 1637 (C=C), 1466, 1390, 1246 (P=O), 1055 (C-O), 1023 (C-O), 953 (P-O) cm^{-1}.

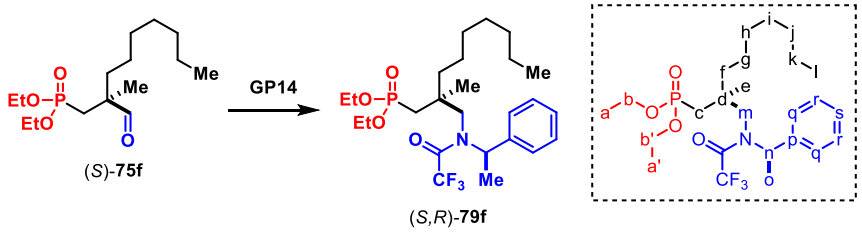


Synthesis of chiral phosphonoaldehyde (*R*)-**75f:** Following the general procedure for ozonolysis of chiral vinyl phosphonates (**GP10**), the chiral vinyl phosphonate (*R*)-**74f** (46 mg, 0.15 mmol) yields the desired product (*R*)-**75f** (38 mg, 83%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = +2.05° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 9.45 (d, *J* = 1.6 Hz, m), 4.13-4.04 (4H, m, b+b'), 2.10-1.92 (2H, m, c), 1.66-1.56 (2H, m, f), 1.35-1.16 (19H, m, a+a'+e+g+h+i+j+k), 0.89-0.86 (3H, m, l) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.42 (d, $^3J_{C\text{-}P}$ = 10 Hz, m), 61.83-61.69 (m, b+b'), 47.16 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 37.00 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 31.94, 31.10 (d, $^1J_{C\text{-}P}$ = 142 Hz, c), 30.19, 29.29, 24.15, 22.79, 20.19 (d, $^3J_{C\text{-}P}$ = 5 Hz, e), 16.56 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a'), 14.25 (l) ppm; ^{31}P

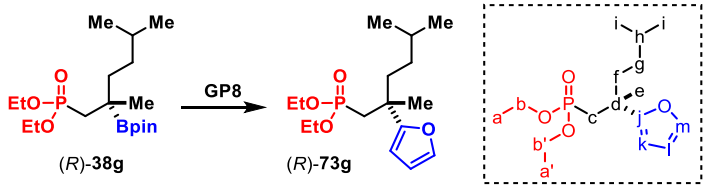
NMR (162 MHz, $CDCl_3$) δ 28.67 ppm; IR (neat) 2923 (sp^2 C-H), 2856 (sp^3 C-H), 1727 (C=O), 1606, 1442, 1244 (P=O), 1053 (C-O), 1025 (C-O), 958 (P-O) cm^{-1}.



Synthesis of chiral γ-amino phosphonate (*R*,*R*)-**79f:** Following the general procedure for the synthesis of chiral γ-amino phosphonates via tandem reductive amination and trifluoroacetylation (**GP14**), the chiral phosphonoaldehyde (*R*)-**75f** (31 mg, 0.10 mmol) yields the diastereomeric γ-amino phosphonate (*R*,*R*)-**79f** (36 mg; 71% overall) as a light yellow oil: TLC analysis (ethyl-acetate/hexanes 3:7) $R_f = 0.5$; $[\alpha]_D^{20} = +9.7^o$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.04-7.32 (5H, m, aryl), 5.33-5.27 (1H, m, n), 4.11-3.92 (4H, m, b+b'), 3.43 (1H, d, *J* = 14.6 Hz, m), 3.21 (1H, d, *J* = 14.6 Hz, m), 1.66-1.17 (23H, m, a+a'+c+f+g+h+i+j+k+o), 0.88-0.85 (3H, m, l), 0.81 (2.91H, s, e; Major diastereomer), 0.704 (0.09H, s, e; Minor diastereomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.71 (d, $^2J_{C\text{-}F}$ = 35 Hz, CF_3C=O), 138.62 (aryl), 129.05 (aryl), 128.66 (aryl), 128.23 (aryl), 61.28-61.19 (m, b+b'), 56.03 (n), 52.87 (d, $^3J_{C\text{-}P}$ = 10 Hz, m), 40.58 (d, $^3J_{C\text{-}P}$ = 6 Hz, f), 36.90 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 34.66 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 32.07, 30.40, 29.56, 24.86 (d, $^3J_{C\text{-}P}$ = 10 Hz, e), 24.12, 22.85, 18.36 (o), 16.59 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a'), 14.31 (l) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 30.28 (3%; Minor diastereomer), 30.14 (97%; Major diastereomer) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.41 (97%; Major diastereomer), –67.45 (3%; Minor diastereomer) ppm; IR (neat) 2989 (aromatic C-H), 2855 (aliphatic C-H), 1689 (C=O), 1578 (C=O), 1453, 1202 (P=O), 1137 (C-F), 1053 (C-O), 1026 (C-O), 956 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{25}H_{41}F_3NO_4P+Na^+$ 530.2618, found 530.2625 *m/z*.

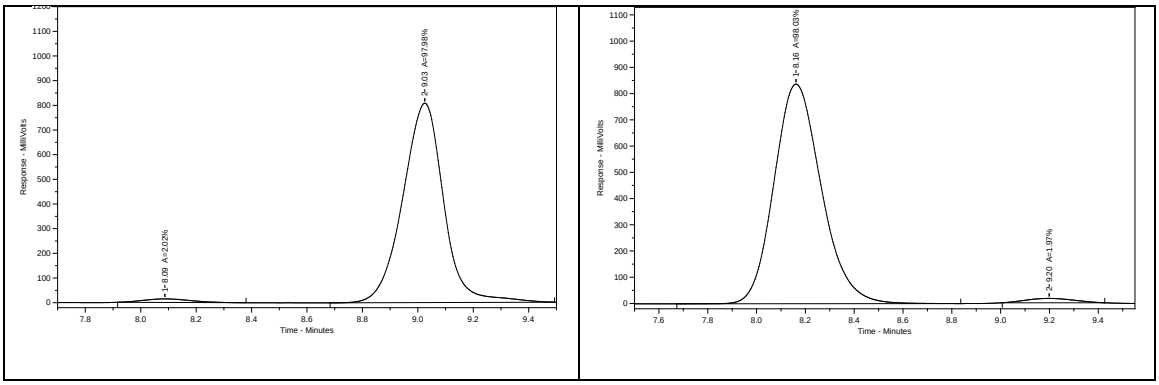


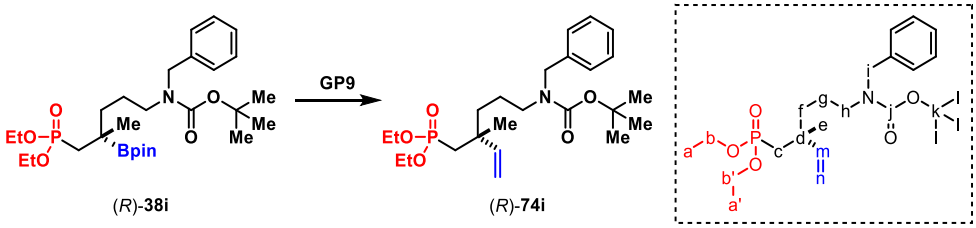
Synthesis of chiral γ-amino phosphonate (*S*,*R*)-**79f:** Following the general procedure for the synthesis of chiral γ-amino phosphonates via tandem reductive amination and trifluoroacetylation (**GP14**), the enantiomeric chiral phosphonoaldehyde (*S*)-**75f** (31 mg, 0.1 mmol) yields the diastereomeric γ-amino phosphonate (*S*,*R*)-**79f** (37 mg; 73% overall) as a light yellow oil: TLC analysis (ethyl-acetate/hexanes 3:7) R_f = 0.5; $[\alpha]_D^{20}$ = +8.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 7.38-7.31 (5H, m, aryl), 5.33-5.27 (1H, m, n), 4.07-3.94 (4H, m, b+b'), 3.52 (1H, d, *J* = 14.4 Hz, m), 3.20 (1H, d, *J* = 14.4 Hz, m), 1.96-0.90 (23H, m, a+a'+c+f+g+h+i+j+k+o), 0.88-0.85 (3H, m, l), 0.81 (0.09H, s, e; Minor diastereomer), 0.704 (2.91H, s, e; Major diastereomer) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.73 (d, $^2J_{C\text{-}F}$ = 35 Hz, CF_3C=O), 138.48 (aryl), 128.95 (aryl), 128.75 (aryl), 128.56 (aryl), 61.45-61.14 (m, b+b'), 56.22 (n), 52.43 (d, $^3J_{C\text{-}P}$ = 10 Hz, m), 40.27 (d, $^3J_{C\text{-}P}$ = 6 Hz, f), 37.02 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 35.24 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 32.09, 30.35, 29.53, 24.66 (d, $^3J_{C\text{-}P}$ = 11 Hz, e), 23.96, 22.87, 18.34 (o), 16.60 (dd, $^3J_{C\text{-}P}$ = 6 Hz, a+a'), 14.31 (l) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) 30.28 (97%; Major diastereomer), 30.14 (3%; Minor diastereomer) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ –67.41 (3%; Minor diastereomer), –67.45 (97%; Major diastereomer) ppm; IR (neat) 2990 (aromatic C-H), 2855 (aliphatic C-H), 1688 (C=O stretch), 1580 (C=O stretch), 1453, 1203 (P=O), 1135 (C-F), 1053 (C-O), 1023 (C-O), 953 (P-O) cm^{-1}.



Synthesis of furan-coupled derivative (*R*)-**73g:** Following the general procedure for cross coupling of chiral tertiary boronic esters with furan (**GP8**), the chiral tertiary boronic ester (*R*)-**38g** (77 mg, 0.20 mmol) yields the furan-coupled derivative (*R*)-**73g** (45 mg, 71%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 7:3) R_f = 0.5; $[\alpha]_D^{20}$ = +3.75° (*c* =1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (1H, d, *J* = 1.2 Hz, m), 6.28-6.27 (1H, m, l), 6.05-6.04 (1H, m, k), 4.01-3.89 (4H, m, b+b'), 2.31-2.07 (2H, m, c), 1.81-1.68 (2H, m, f), 1.48-1.42 (4H, overlap of singlet & multiplet, e+h), 1.29-1.20 (6H, m, a+a'), 1.07-0.82 (8H, m, g+i) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.35 (d, $^3J_{C\text{-}P}$ = 9.75 Hz, j), 140.78 (m), 109.80 (l), 104.68 (k), 61.20-61.04 (m, b+b'), 39.60 (d, $^3J_{C\text{-}P}$ = 11.25 Hz, f), 36.55 (d, $^1J_{C\text{-}P}$ = 138.75 Hz, c), 35.15 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 33.16 (d, $^4J_{C\text{-}P}$ = 1.5 Hz, g), 28.34 (h), 23.49 (d, $^3J_{C\text{-}P}$ = 3.75 Hz, e), 22.60 (i), 16.37 (m, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.64 ppm; IR (neat) 2954.90 (aromatic C-H), 2870.22 (aliphatic C-H), 1714.51 (furyl C-O), 1289.93 (P=O), 1053.23 (C-O), 954.55 (P-O), 729.68 cm^{-1}; HRMS (ESI) calculated for $C_{16}H_{29}O_4P$ 316.1803, found 316.1800 *m/z*. Enantiomer ratio = 98:2, determined via chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile phase = 1:1 hexanes : isopropanol; Flow rate = 1.0 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

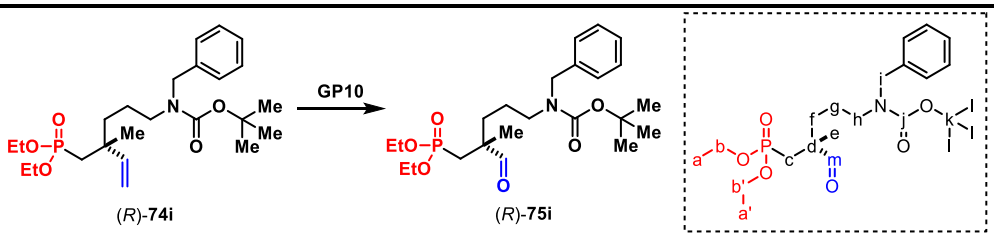
(a). R:S = 2 : 98, cross coupling of (*R*)-**38g**:	(b). R:S = 2 : 98, cross coupling of (*S*)-**38g**:



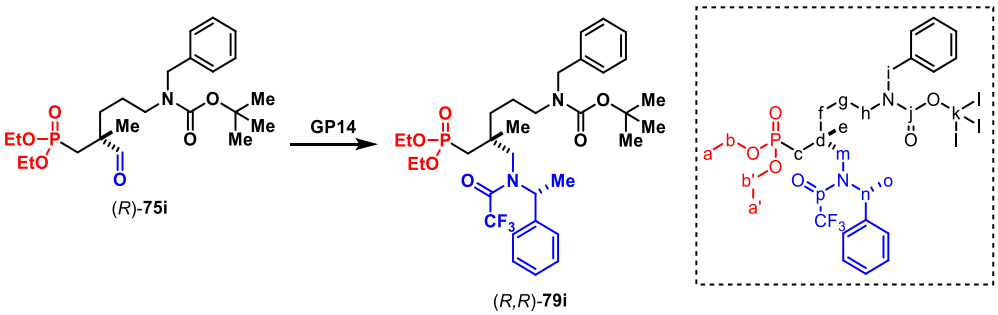


Synthesis of chiral vinyl phosphonate (*R*)-**74i:** Following the general procedure for vinylation of chiral tertiary boronic esters (**GP9)**, the chiral tertiary boronic ester (*R*)-**38i** (56 mg, 0.10 mmol) yields the chiral vinyl phosphonate (*R*)-**74i** (40 mg, 88%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = –3.50° (*c* =1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d6, 353K) δ 7.35-7.23 (5H, m, aryl), 5.83 (1H, dd, *J* = 17.4, 11.2 Hz, m), 4.97-4.91 (2H, m, n), 4.38 (2H, s, i), 4.01-3.94 (4H, m, b+b'), 3.16-3.10 (2H, br m, h), 1.78 (2H, d, *J* = 18.4 Hz, c), 1.46-1.41 (13H, m, f+g+l), 1.24 (6H, t, *J* = 7.0 Hz, a+a'), 1.11 (3H, s, e) ppm; ^{13}C NMR (100 MHz, DMSO-d6, 353K) δ 154.57 (j), 145.85 (d, $^3J_{C\text{-}P}$ = 10 Hz, m), 138.36 (aryl), 127.78 (aryl), 126.77 (aryl), 126.37 (aryl), 110.83 (n), 78.24 (k), 60.10 (dd, $^2J_{C\text{-}P}$ = 7.0, 4.0 Hz, b+b'), 49.51 (i), 46.61 (h), 37.34 (d, $^3J_{C\text{-}P}$ = 9 Hz, f), 37.15 (d, $^2J_{C\text{-}P}$ = 2 Hz, d), 35.58 (d, $^1J_{C\text{-}P}$ = 137 Hz, c), 27.65 (l), 23.60 (d, $^3J_{C\text{-}P}$ = 7.0 Hz, e), 22.31 (g), 15.64 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, DMSO-d6, 353K) δ 28.48 ppm; IR (neat) 2976 (aromatic C-H), 2930 (aliphatic C-H), 1689 (C=O), 1454, 1413, 1390, 1364, 1242 (P=O), 1162 (C-N), 1054 (C-O), 1025 (C-O), 955 (P-O) cm^{-}

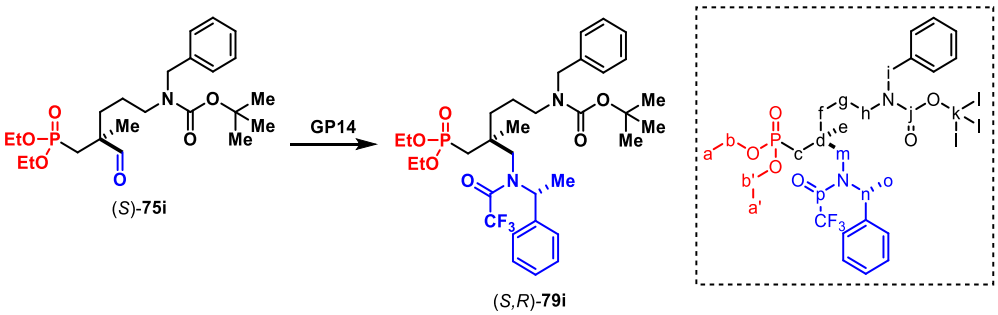
[1]. [*Note: NMR data for this molecule were recorded at a higher temperature (80°C, 353K) to speed up the interconversions between the tertiary amide rotamers at the NMR time scale which resulted in clean spectra. Room temperature NMR shows broadened peaks which resulted due to slow interconversions between the rotamers.*]



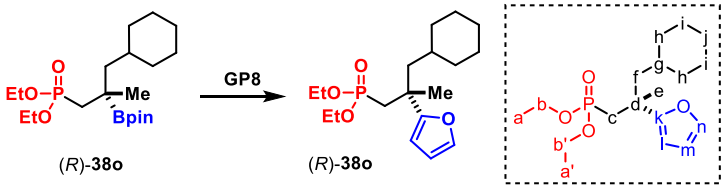
Synthesis of chiral phosphonoaldehyde (*R*)-**75i:** Following the general procedure for ozonolysis of chiral vinyl phosphonates (**GP10**), the chiral vinyl phosphonate (*R*)-**74i** (35 mg, 75 μmol) yields the chiral phosphonoaldehyde (*R*)-**75i** (27 mg, 78%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = –2.50° (*c* =1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, DMSO-d6, 353K) δ 9.42 (1H, s, m), 7.35-7.23 (5H, m, aryl), 4.38 (2H, s, i), 4.03-3.96 (4H, s, b+b'), 3.13 (2H, t, *J* = 7.0 Hz, h), 2.06-1.88 (2H, m, c), 1.53-1.36 (13H, m, f+g+l), 1.25 (6H, t, *J* = 7.0 Hz, a+a'), 1.11 (3H, s, e) ppm; ^{13}C NMR (100 MHz, DMSO-d6, 353K) δ 204.48 (d, $^3J_{C\text{-}P}$ = 9.0 Hz, m), 155.65 (j), 139.40 (aryl), 128.83 (aryl), 127.84 (aryl), 127.44 (aryl), 79.47 (k), 61.58 (d, $^2J_{C\text{-}P}$ = 5.0 Hz, b+b'), 50.67 (i), 47.55 (h), 46.77 (d), 33.90 (d, $^3J_{C\text{-}P}$ = 10 Hz, f), 31.76 (d, $^1J_{C\text{-}P}$ = 139 Hz, c), 28.72 (l), 22.95 (g), 19.92 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, e), 16.59 (d, $^3J_{C\text{-}P}$ = 5.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, DMSO-d6, 353K) δ 27.70 ppm; IR (neat) 2977 (aromatic C-H), 2915 (aliphatic C-H), 1727 (aldehyde C=O), 1687 (carbamate C=O), 1454, 1414, 1365, 1241 (P=O), 1160 (C-N), 1052 (C-O), 1023 (C-O), 958 (P-O) cm^{-1}.



Synthesis of chiral γ-amino phosphonate (*R*,*R*)-**79i:** Following the general procedure for the synthesis of chiral γ-amino phosphonates via tandem reductive amination and trifluoroacetylation (**GP14**), the chiral phosphonoaldehyde (*R*)-**75i** (23 mg, 50 μmol) yields the diastereomeric γ-amino phosphonate (*R*,*R*)-**79i** (24 mg; 73% overall) as a light yellow oil: TLC analysis (ethyl-acetate/hexanes 3:7) R_f = 0.4; $[\alpha]_D^{20}$ = +11.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d6, 373K) δ 7.42-7.23 (10H, m, aryl), 5.13 (1H, br s, n), 4.38 (2H, s, i), 3.98-3.89 (4H, m, b+b'), 3.47 (1H, d, *J* = 14.6 Hz, m), 3.29 (1H, d, *J* = 14.6 Hz, m), 3.10 (2H, t, *J* = 7.2 Hz, h), 1.70 (3H, d, *J* = 6.8 Hz, o), 1.60-1.33 (15H, m, c+f+g+l), 1.22 (6H, td, *J* = 7.01, 4.10 Hz, a+a'), 0.87 (3H, s, e) ppm; ^{13}C NMR (100 MHz, DMSO-d6, 373K) δ 154.45 (j), 138.47 (aryl), 138.26 (aryl), 127.93 (aryl), 127.62 (aryl), 127.27 (aryl), 126.64 (aryl), 127.59 (aryl), 126.22 (aryl), 78.18 (k), 60.10 (d, $^2J_{C\text{-}P}$ = 7 Hz, b+b'), 49.47 (i), 46.56 (h), 36.08 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 35.92 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, f), 33.91 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 27.52 (l), 23.52 (d, $^3J_{C\text{-}P}$ = 9.0 Hz, e), 21.82 (g), 17.26 (o), 51.41 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, DMSO-d6, 373K) δ 28.53 ppm; ^{19}F NMR (376 MHz, DMSO-d6, 373K) δ -66.54 ppm; IR (neat) 2978 (aromatic C-H), 2850 (aliphatic C-H), 1700 (amide C=O stretch), 1689 (carbamate C=O stretch), 1455, 1276 (P=O), 1142 (C-F), 1053 (C-O), 1027 (C-O), 959 (P-O) cm^{-1}; HRMS (ESI) calculated for $C_{33}H_{48}F_3N_2O_6P$+Na^+ 679.3100, found 679.3109 *m/z*. Diastereomer ratio is estimated to be >20:1 by comparison of the NMRs with the diastereomeric (*S*,*R*)-**79i**.

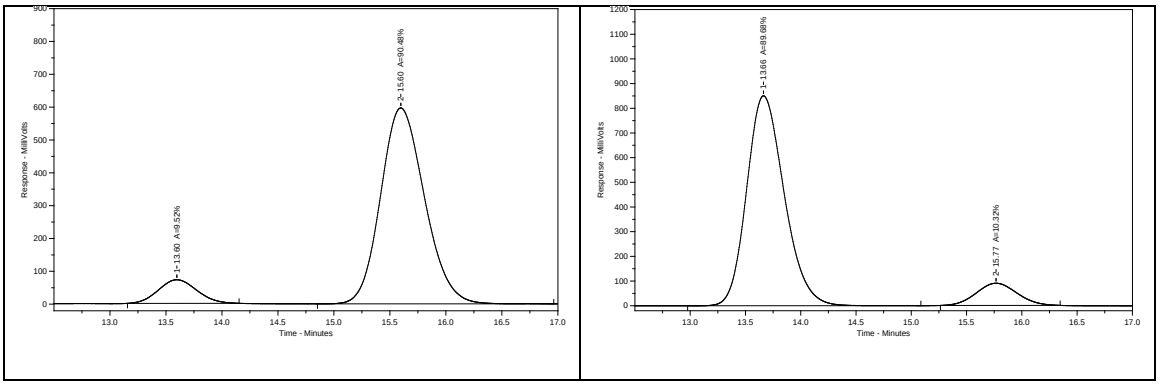


Synthesis of chiral γ-amino phosphonate (*S*,*R*)-**79i:** Following the general procedure for the synthesis of chiral γ-amino phosphonates via tandem reductive amination and trifluoroacetylation (**GP14**), the enantiomeric chiral phosphonoaldehyde (*S*)-**75i** (23 mg, 50 μmol) yielded the diastereomeric γ-amino derivative (*S*,*R*)-**79i** (25 mg; 76% overall) as a light yellow oil: TLC analysis (ethyl-acetate/hexanes 3:7) R_f = 0.4; $[\alpha]_D^{20}$ = +10.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d6, 373K) δ 7.39-7.22 (10H, m, aryl), 5.12 (1H, br s, n), 4.37 (2H, s, i), 3.99-3.90 (4H, m, b+b'), 3.43 (1H, d, *J* = 14.6 Hz, m), 3.35 (1H, d, *J* = 14.6 Hz, m), 3.04 (2H, t, *J* = 7.2 Hz, h), 1.85-1.52 (5H, m, o+c), 1.46-1.35 (13H, m, f+g+l), 1.24-1.96 (6H, m, a+a'), 0.84 (3H, s, e) ppm; ^{13}C NMR (100 MHz, DMSO-d6, 373K) δ 154.46 (j), 138.50 (aryl), 138.28 (aryl), 127.92 (aryl), 127.65 (aryl), 127.27 (aryl), 126.74 (aryl), 126.64 (aryl), 126.25 (aryl), 78.20 (k), 60.16 (d, $^2J_{C\text{-}P}$ = 7 Hz, b+b'), 49.45 (i), 46.56 (h), 36.12 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 33.88 (d, $^1J_{C\text{-}P}$ = 136 Hz, c), 27.56 (l), 23.39 (d, $^3J_{C\text{-}P}$ = 9.0 Hz, e), 21.78 (g), 17.32 (o), 51.44 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, DMSO-d6, 373K) δ 28.61 ppm; ^{19}F NMR (376 MHz, DMSO-d6, 373K) δ -66.51 ppm; IR (neat) 2979 (aromatic C-H), 2849 (aliphatic C-H), 1701 (amide C=O stretch), 1689 (carbamate C=O stretch), 1455, 1276 (P=O), 1142 (C-F), 1053 (C-O), 1029 (C-O), 958 (P-O) cm^{-1}; Diastereomer ratio is estimated to be >20:1 by comparison of the NMRs with the diastereomeric (*R*,*R*)-**79i**.

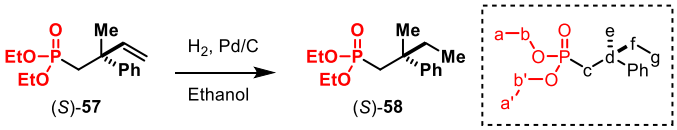


Synthesis of the furan-coupled derivative (*R*)-**38o:** Following the general procedure for cross coupling of chiral tertiary boronic esters with furan (**GP8**), the chiral tertiary boronic ester (*R*)-**38o** (40 mg, 0.10 mmol) yields the furan-coupled derivative (*R*)-**38o** (22 mg, 65%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 6:4) R_f = 0.5; $[\alpha]_D^{20}$ = +3.3° (*c* =1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (1H, br s, n), 6.27 (1H, br s, m), 6.05 (1H, d, *J* = 3.0 Hz, l), 4.03-3.81 (4H, m, b+b'), 2.34-2.02 (2H, m, c), 1.78-0.93 (22H, m, a+a'+e+f+g+h+i+j) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.23 (d, $^3J_{C\text{-}P}$ = 9 Hz, k), 140.44 (n), 110.09 (m), 104.69 (l), 61.11 (d, $^2J_{C\text{-}P}$ = 6.75, 3.75 Hz, b+b'), 49.79 (d, $^3J_{C\text{-}P}$ = 12.75 Hz, f), 37.47 (d, $^1J_{C\text{-}P}$ = 138 Hz, c), 37.06 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 35.29, 33.98, 33.88 (d, $^4J_{C\text{-}P}$ = 2.25 Hz, g), 26.49, 26.39, 26.24, 23.39 (d, $^3J_{C\text{-}P}$ = 3 Hz, e), 16.40 (d, $^3J_{C\text{-}P}$ = 3 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.51 ppm; IR (neat) 2919 (aromatic C-H), 2949 (aliphatic C-H), 1505 (furyl C-O), 1242 (P=O), 1053 (C-O), 1024 (C-O), 954 (P-O), 728 cm^{-1}; HRMS (ESI) calculated for $C_{18}H_{31}O_4P$ 342.1960, found 342.1957 *m/z*. Enantiomer ratio = 90:10, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 1:1 hexanes : isopropanol; Flow rate = 1.0 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a). R:S = 90 : 10, cross coupling of (*R*)-**38o**:	(b). R:S = 10 : 90, cross coupling of (*S*)-**38o**:

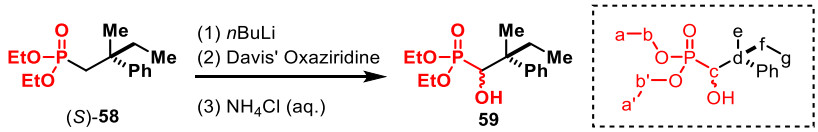


5.9. Oxidations leading to α-hydroxy and oxophosphonates and their synthetic utility



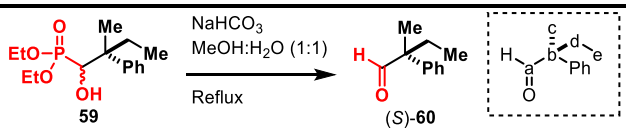
Synthesis of phosphonate (*S*)-58 via hydrogenation of vinylated derivative (*S*)-57: A mixture of vinylated derivative (*S*)-**57** (282 mg, 1.00 mmol) and 10% Pd on activated carbon (20 mg, 2.0 mol% Pd loading) in ethanol (10 mL) is stirred under a hydrogen atmosphere (balloon pressure) for 6 hours. Afterwards, the mixture is concentrated under reduced pressure and the concentrate is dissolved in ethyl acetate (20 mL) and is filtered over a bed of celite to get rid of insoluble materials. The celite bed is washed with ethyl acetate (2 x 20 mL) and the combined filtrates were concentrated under reduced pressure to yield the reduced product (*S*)-**58** (270 mg, 95%): TLC analysis (ethyl acetate/hexanes 3:1) R_f = 0.5; $[\alpha]_D^{20}$ = -5° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.19 (5H, m, aryl), 3.92-3.66 (4H, m, b+b'), 2.29-2.10 (2H, m, c), 1.92-1.76 (2H, m, f), 1.56 (3H, s, e), 1.18 (3H, t, *J* = 7.0 Hz, a or a'), 1.12 (3H, t, *J* = 7.0 Hz, a or a'), 0.66 (3H, t, *J* = 7.4 Hz, g) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.67 (d, $^3J_{C\text{-}P}$ = 8 Hz, ipso C of phenyl group), 128.19 (aryl), 126.51 (aryl), 125.98 (aryl), 61.18-61.02 (m, b+b'), 39.68 (d, $^1J_{C\text{-}P}$ = 138 Hz,

c), 39.66 (d, $^{2}J_{C\text{-}P}$ = 3 Hz, d), 36.88 (d, $^{3}J_{C\text{-}P}$ = 14 Hz, f), 24.09 (d, $^{3}J_{C\text{-}P}$ = 4 Hz, f), 16.50-16.40 (m, a+a'), 8.81 (g) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.12 ppm; IR (neat) 3021 (aromatic C-H), 2915 (aliphatic C-H), 1251 (P=O), 1015 (C-O), 940 (P-O) cm^{-1}.



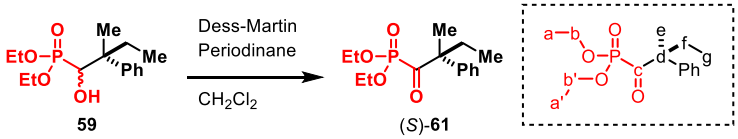
Synthesis of α-hydroxyphosphonate 59: This transformation is carried out with few modifications of the original procedure[29] reported by Weimer as follows: A solution of the chiral phosphonate (*S*)-**58** (213 mg, 0.75 mmol, 1.00 eq) in dry THF (15 mL) is cooled down to -78°C using a dry ice-acetone bath and a solution of *n*BuLi in hexanes (2.5M; 0.6 mL, 1.5 mmol, 2.0 eq) is added drop-wise. The resultant mixture is stirred at -78°C for 5 minutes and then the cooling bath is removed and the mixture is stirred at room temperature for an hour. The mixture is re-cooled to -78°C and a solution of Davis' Oxaziridine (392 mg, 1.50 mmol, 2.00 eq) in dry THF (5 mL) is added drop-wise. The resultant mixture is maintained at -78°C for a total of *ca.* 3 hours and then quenched with the addition of saturated aqueous NH_4Cl solution (25 mL) at -78°C. The resultant frozen mixture is allowed to slowly warm up to room temperature over 1 hour and is then extracted with ethyl acetate (25 mL x 3). The combined organics are washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. Flash chromatography over silica gel (ethyl acetate/hexanes 6:4) affords the product as an opaque semi-solid material (186 mg, 83%; formed as a ~2:1 mixture of diastereomers): TLC analysis (ethyl acetate/hexanes 6:4) R_f = 0.5; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.45-7.23 (5H, m, aryl), 4.10-3.75 (5H, m, b+b'+c), 2.11-2.07 (1H, m, f), 2.00-1.97 (1H, m, f), 1.57 (0.9H, s, e (minor diastereomer)), 1.53 (2.1H, s, e (major diastereomer)), 1.30 (0.98H, t, *J* = 7.0 Hz, a or a' (minor diastereomer)),

1.21 (0.89H, t, J = 7.0 Hz, a or a' (minor diastereomer)), 1.17 (2.01H, t, J = 7.0 Hz, a or a' (major diastereomer)), 1.11 (1.99H, t, J = 7.0 Hz, a or a' (major diastereomer)), 0.70-0.66 (3H, m, g) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 143.57 (d, $^3J_{C\text{-}P}$ = 10 Hz, ipso C of aromatic ring (minor diastereomer)), 143.28 (d, $^3J_{C\text{-}P}$ = 10 Hz, ipso C of aromatic ring (major diastereomer)), 128.43 (meta C's of aromatic ring (minor diastereomer)), 128.20 (meta C's of aromatic ring (major diastereomer)), 127.74 (ortho C's of aromatic ring (major diastereomer)), 127.66 (ortho C's of aromatic ring (minor diastereomer)), 126.61 (para C of aromatic ring (minor diastereomer)), 126.46 (para C of aromatic ring (major diastereomer)), 76.93 (d, $^1J_{C\text{-}P}$ = 155 Hz, c (major diastereomer)), 76.66 (d, $^1J_{C\text{-}P}$ = 155 Hz, c (minor diastereomer)), 62.43 (d, $^2J_{C\text{-}P}$ = 7 Hz, b or b' (minor diastereomer)), 62.43 (d, $^2J_{C\text{-}P}$ = 7 Hz, b or b' (major diastereomer)), 62.27 (d, $^2J_{C\text{-}P}$ = 8 Hz, b or b' (minor diastereomer)), 62.19 (d, $^2J_{C\text{-}P}$ = 6 Hz, b or b' (major diastereomer)), 31.26-31.18 (m, f), 19.27 (d, $^3J_{C\text{-}P}$ = 3 Hz, e (minor diastereomer)), 18.76 (d, $^3J_{C\text{-}P}$ = 3 Hz, e (major diastereomer)), 16.62 (d, $^3J_{C\text{-}P}$ = 6 Hz, a or a' (minor diastereomer)), 16.56 (d, $^3J_{C\text{-}P}$ = 6 Hz, a or a' (minor diastereomer)), 16.48 (d, $^3J_{C\text{-}P}$ = 6 Hz, a or a' (major diastereomer)), 16.41 (d, $^3J_{C\text{-}P}$ = 6 Hz, a or a' (major diastereomer)), 8.41 (g, minor diastereomer), 8.29 (g, major diastereomer) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.43 (67%, major diastereomer), 23.32 (33%, minor diastereomer) ppm; IR (neat) 3256 (O-H), 2971 (aromatic C-H), 2906 (aliphatic C-H), 1212 (P=O), 1026 (C-O), 975 (P-O), 699 cm^{-1}.



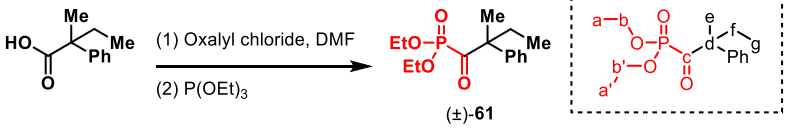
Synthesis of aldehyde (*S*)-60 from α-hydroxyphosphonate 59:[11] This transformation is carried out with some modifications of the original procedure[30] reported by Spilling and

coworkers as follows: A stirred suspension of hydroxyphosphonate **59** (60 mg, 0.2 mmol, 1 eq) and sodium bicarbonate (84 mg, 1.0 mmol, 5 eq) in 1:1 MeOH:H_2O (5 mL) is refluxed for 1 hour. Following this, the mixture is diluted with ethyl acetate (25 mL) and the aqueous layer separated. The organic layer is washed with brine (10 mL), dried over Na_2SO_4 and concentrated in vacuum to afford pure aldehyde (*S*)-**60** (29 mg, 89%): TLC analysis (ethyl acetate/hexanes 1:40) $R_f = 0.5$; $[\alpha]_D^{20} = +9.2^o$ (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (1H, s, aldehyde H), 7.42-7.27 (5H, m, aryl), 2.07-1.88 (2H, m, d), 1.46 (3H, s, c), 0.82 (3H, t, *J* = 7.4 Hz, e) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.91 (a), 140.14 (aryl), 128.98 (aryl), 127.39 (aryl), 127.33 (aryl), 54.47 (b), 28.73 (d), 18.45 (c), 8.56 (e) ppm; IR (neat) 3057 (aldehyde C-H), 2968 (aromatic C-H), 2936 (aliphatic C-H), 1722 (C=O), 1494 (aromatic C=C), 1446 (aromatic C=C) cm^{-1}. Upon reduction with $NaBH_4$ in MeOH, aldehyde (*S*)-**60** is transformed to the alcohol (*S*)-(+)-**62** (*vide infra*), which unambiguously confirmed its absolute configuration to be *"S"* based on the positive value of the optical rotation of (*S*)-(+)-**62**. Enantiomer ratio of aldehyde (*S*)-**60** is determined via chiral HPLC analysis of the formed alcohol **62** (upon reduction using $NaBH_4$): 95:5 er (*vide infra*).



Synthesis of α-oxophosphonate (*S*)-**61:** A suspension of hydroxyphosphonate **59** (60 mg, 0.2 mmol, 1 eq) and Dess-Martin Periodinane (170 mg, 0.4 mmol, 2 eq) in dichloromethane (5 mL) is stirred at room temperature for 3 hours. The completion of the reaction is indicated by the disappearance of the diastereomeric hydroxyphosphonate peaks at ~25 ppm and appearance of a new peak at -3 ppm indicative of the presence of oxophosphonate in the reaction mixture. The mixture is diluted with ethyl acetate (25 mL), washed with

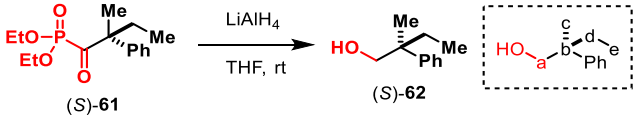
saturated $NaHCO_3$ (10 mL), saturated $Na_2S_2O_3$ (10 mL) and brine (5 mL). The resultant organic extract is dried over Na_2SO_4 and concentrated in vacuum. Flash chromatography on silica gel (ethyl acetate/hexanes 1:1) affords the desired product (*S*)-**61** as a colorless viscous oil (55 mg, 92%) : TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +54.8° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (5H, m, aryl), 3.94-3.72 (4H, m, b+b'), 2.17-1.96 (2H, m, f), 1.60 (3H, s, e), 1.13 (6H, m, a+a'), 0.75 (3H, t, *J* = 7.4 Hz, g) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.14 (d, $^1J_{C\text{-}P}$ = 155 Hz, c), 139.44 (aryl), 128.73 (aryl), 127.50 (aryl), 127.37 (aryl), 63.48-63.23 (m, b+b'), 57.41 (d, $^2J_{C\text{-}P}$ = 51 Hz, d), 29.49 (f), 19.31 (e), 16.29 (dd, $^3J_{C\text{-}P}$ = 5 Hz, a+a'), 8.49 (g) ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ -3.21 ppm; IR (neat) 2878 (aromatic C-H), 2936 (aliphatic C-H), 1678 (C=O), 1496 (aromatic C=C), 1446 (aromatic C=C), 1255 (P=O), 1014 (C-O), 967 (P-O) cm^{-1}. HRMS (EI) calculated for $C_{15}H_{23}O_4P$ = 298.1334, found 298.1329 *m/z*.



(±)-**61**

Synthesis of oxophosphonate (±)-61: To a solution of (±)-2-methyl-2-phenylbutanoic acid (1.00 g, 5.61 mmol, 1.00 eq.) in dry dichloromethane (10 mL) is added oxalyl chloride (0.72 mL, 8.42 mmol, 1.5 eq.) dropwise at 0°C. After complete addition of oxalyl chloride, a drop of DMF is added and the reaction mixture is stirred at room temperature for a total of 2 hours. Following this, the reaction mixture is concentrated in vacuum to get rid of the volatiles and the concentrate is dissolved in dry dichloromethane (10 mL). Triethylphosphite (0.96 mL, 5.61 mmol, 1.50 eq) is added drop-wise to the solution of the intermediate acyl chloride in dichloromethane at room temperature.[31] The completion of the modified Michaelis-Arbuzov Rearrangement (*ca.* 1 hour) is determined by the ^{31}P

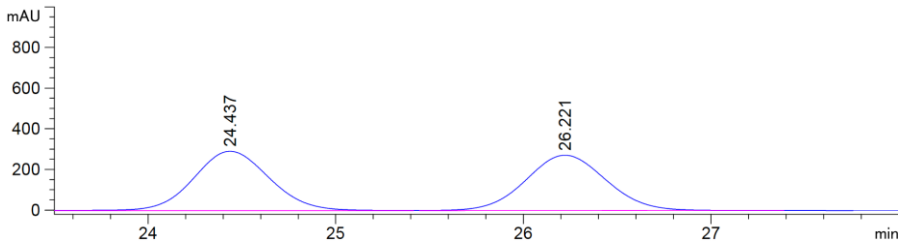
NMR analysis of the crude reaction mixture following disappearance of the triethylphosphite peak at ~130 ppm and appearance of a new peak at -3 ppm corresponding to the oxophosphonate product. Afterwards the reaction mixture is concentrated under reduced pressure. Flash chromatography on silica gel (ethyl acetate/hexanes 1:1) affords the desired product (±)-**61** as a colorless viscous oil (1.49 g, 89%).



Synthesis of alcohol (*S*)-62:[11] This transformation is carried out with some modifications of the original reported procedure[32] by Yamamoto and coworkers as follows: To a solution of acylphosphonate (*S*)-**61** (60 mg, 0.2 mmol, 1 eq) in THF (2 mL) is added lithium aluminum hydride (30 mg, 0.8 mmol, 4 eq) at 0°C. The resultant mixture is stirred for 2 hours at room temperature. The disappearance of the peak corresponding to oxo-phosphonate in crude ^{31}P NMR (~ -3 ppm) is indicative of reaction completion. The reaction mixture is cooled down to 0°C and is quenched with the addition of 2M HCl till pH 2. The resultant mixture is extracted with diethyl ether (3 mL x 4), the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuum to yield the desired product (*S*)-**62** (29 mg, 89%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 2:8) R_f = 0.5; $[\alpha]_D^{20}$ = +8.8° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (4H, m, aryl), 7.28-7.22 (1H, m, aryl), 3.75 (1H, d, *J* = 10.8 Hz, a), 3.57 (1H, d, *J* = 10.8 Hz, a), 1.89-1.80 (1H, m, d), 1.64-1.55 (1H, m, d), 1.37 (3H, s, c), 1.29 (1H, br s, OH), 0.75 (3H, t, *J* = 7.4 Hz, e) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 144.78 (aryl), 128.62 (aryl), 127.04 (aryl), 126.30 (aryl), 72.59 (a), 43.89 (b), 31.07 (d), 21.14 (c), 8.42 (e) ppm; IR (neat) 3300 (O-H), 2920 (aromatic C-H), 2851 (aliphatic C-H), 1495 (aromatic

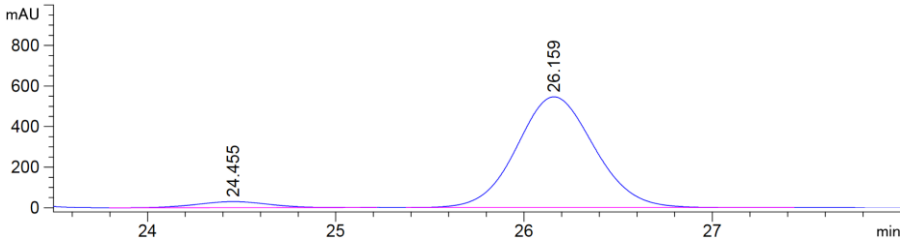
C=C), 1463 (aromatic C=C), 1034, 756 cm^{-1}. Enantiomer ratio also determined by chiral HPLC analysis: 95:5. HPLC conditions:[11] Stationary phase = CHIRALPAK IB; Mobile Phase = 99.5:0.5 Hexanes:Isopropanol; Flow rate = 0.5 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a) Racemate:

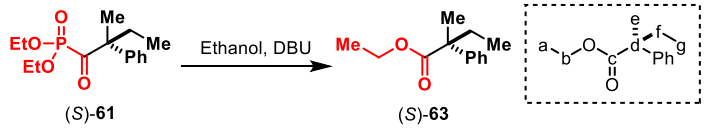


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	24.437	VB	0.4381	8230.35547	50.3273
2	26.221	BB	0.4642	8123.31299	49.6727

(b) R:S = 5:95. CAHB of **5a** with (*R*,*R*)-**T2**, followed by transformations to yield (*S*)-**62**.

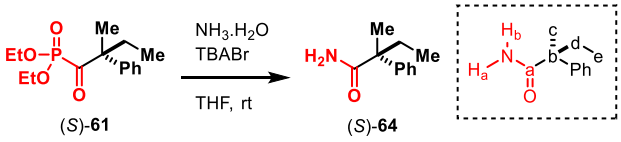


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	24.455	VB	0.4110	781.75848	4.7521
2	26.159	BB	0.4440	1.56692e4	95.2479



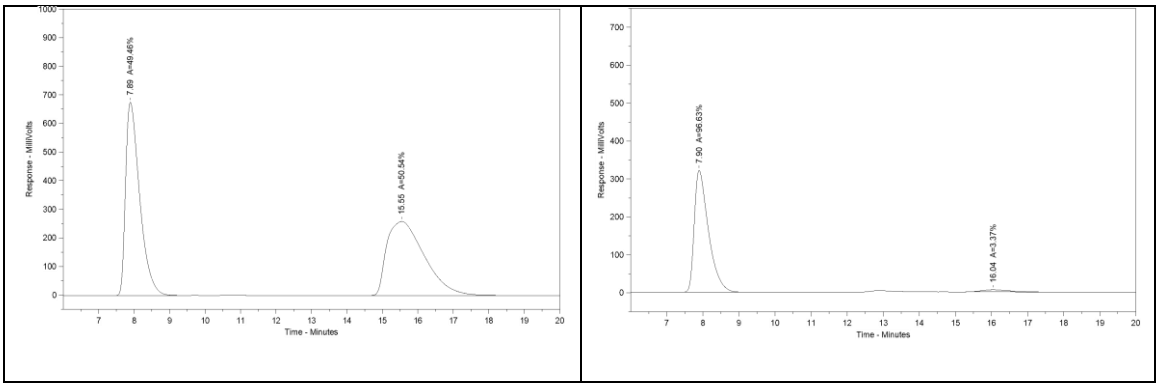
(*S*)-**61** (*S*)-**63**

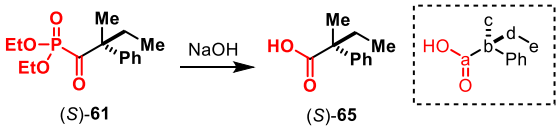
Synthesis of ethyl ester (*S*)-63: This transformation is carried out with some modifications of the original procedure[14] reported by Yamamoto and coworkers as follows: To a solution of acylphosphonate (*S*)-**61** (60 mg, 0.2 mmol, 1 eq) in anhydrous ethanol (1 mL), DBU (30 µL, 0.2 mmol, 1 eq) is added at room temperature. The completion of the reaction (*ca.* 30 min) is indicated by the disappearance of the oxophosphonate peak at -3 ppm and appearance of the diethylphosphite peak at ~8 ppm. The reaction mixture is concentrated under reduced pressure and is dissolved in 10% ethyl acetate in hexanes (2 mL) and is filtered over a small plug of silica gel. The plug is subsequently washed with 2 more portions of the eluent (2 mL each time) and the combined filtrates are concentrated under reduced pressure to afford the ethyl ester (*S*)-**63** as a colorless oil (39 mg, 95%): TLC analysis (ethyl acetate/hexanes 1:20) R_f = 0.6; $[\alpha]_D^{20}$ = +6.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (5H, m, aryl), 4.16 (2H, q, *J* = 7.2 Hz, b), 2.18-2.09 (1H, m, f), 2.02-1.93 (1H, m, f), 1.55 (3H, s, e), 1.21 (3H, t, *J* = 7.2 Hz, a), 0.86 (3H, t, *J* = 7.2 Hz, g) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.43 (c), 144.24 (aryl), 128.45 (aryl), 126.70 (aryl), 126.23 (aryl), 60.83 (b), 50.75 (d), 31.98 (f), 22.42 (e), 14.28 (a), 9.33 (g) ppm; IR (neat) 2975 (aromatic C-H), 2938 (aliphatic C-H), 1724 (C=O), 1496 (aromatic C=C), 1446 (aromatic C=C), 1031 (C-O) cm^{-1}. Ester (*S*)-**63** is transformed to the carboxylic acid (*S*)-**65** (*vide infra*) via hydrolysis using LiOH in H_2O. The formed carboxylic acid was derivatized to the L-phenyl-alanine ethyl ester derivative and the dr of the same was found to be 96:4 via ^{1}H NMR analysis. Therefore, er of ethyl ester (*S*)-**63** = 96:4.



Synthesis of acetamide (*S*)-64:[33] This transformation is carried out with some modifications of the original reported procedure[34] by Liu and Feng as follows: To a solution of acylphosphonate (*S*)-**61** (45 mg, 0.15 mmol, 1 eq) in THF (1 mL) is added NH_3 solution in H_2O (32%, 3 mL) under stirring. To the resultant mixture is added tetrabutylammonium bromide (TBABr; 4.8 mg, 15 μmol, 0.1 eq) and the reaction mixture is stirred at room temperature for 9 hours. Afterwards, the mixture is subjected to high vacuum to get rid of ammonia and the resultant mixture is extracted with ethyl acetate (5 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuum. Flash chromatography over silica gel (ethyl acetate/hexanes 1:1) affords the desired product (*S*)-**64** (23 mg, 85%) as colorless waxy solid: TLC analysis (ethyl acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +14° (*c* = 1.0, C_6H_6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.22 (5H, m, aryl), 6.14 (1H, br s, NH_a or NH_b), 5.25 (1H, br s, NH_a or NH_b), 2.11-1.97 (2H, m, d), 1.53 (3H, s, c), 0.82 (3H, t, *J* = 7.4 Hz, e) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 180.06 (a), 144.07 (aryl), 128.73 (aryl), 127.03 (aryl), 126.90 (aryl), 50.83 (b), 31.57 (d), 23.19 (c), 8.94 (e) ppm; IR (neat) 3400 (N-H), 3203 (N-H), 2982 (aromatic C-H), 2969 (aliphatic C-H), 1648 (C=O), 1494 (aromatic C=C), 1459 (aromatic C=C), 1363, 694 cm^{-1}. Enantiomer ratio = 97:3, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AS-H; Mobile Phase = 60:40 Hexanes:Isopropanol; Flow rate = 1.25 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

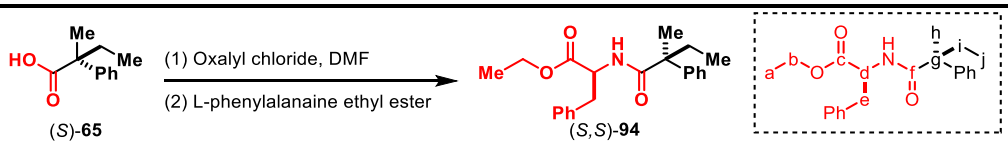
(a) Racemate:	(b) R:S = 3:97. CAHB of **5a** with (*R*,*R*)-**T2**, followed by transformations to **64**:





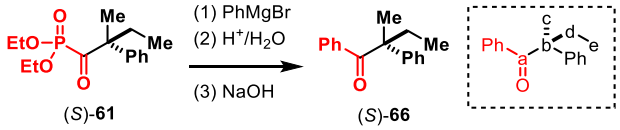
Synthesis of carboxylic acid (*S*)-(+)-**65:**[35] This transformation is carried out with some modifications of the original procedure[14] reported by Yamamoto and coworkers as follows: To a solution of acylphosphonate (*S*)-**61** (60 mg, 0.2 mmol, 1 eq) in tetrahydrofuran (0.5 mL), 2M aqueous NaOH solution (0.5 mL, 1 mmol, 5 eq.) is added and the resultant biphasic mixture is stirred for 3 hours at room temperature. The completion of the reaction is indicated by the disappearance of the oxophosphonate peak at -3 ppm and appearance of the diethylphosphite peak at ~8 ppm. Afterwards, the reaction mixture is acidified to pH 1 using 2N HCl and the resultant mixture is extracted with dichloromethane (10 mL x 3). The combined organic extracts are washed with brine (5 mL), dried over Na_2SO_4 and concentrated in vacuum to afford pure carboxylic acid (*S*)-**65** (32.5 mg, 91%): TLC analysis (ethyl acetate/hexanes 2:8) R_f = 0.5; $[\alpha]_D^{20}$ = +10.2° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (1H, br s, COOH), 7.34-7.20 (5H, m, aryl), 2.03-1.84 (2H, m, d), 1.43 (3H, s, c), 0.78 (3H, t, *J* = 7.4 Hz, e) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.15 (COOH), 144.29 (aryl), 126.41 (aryl), 126.02 (aryl), 49.90 (b), 31.37 (d), 22.16 (c), 9.23 (e) ppm; IR (neat) 3200 (br, O-H), 2976 (aromatic C-H), 2941 (aliphatic C-H), 1690

(C=O), 1495 (aromatic C=C), 1445 (aromatic C=C), 1155 (C-O) cm^{-1}. The above carboxylic acid, (*S*)-**65** is transformed into the amino acid derivative **94** (*vide infra*) and the dr (96:4) is determined via ^1H NMR analysis. Therefore, er of the carboxylic acid (*S*)-**65** = 96:4.



Synthesis of the amino acid derivative 94: To a stirred solution of the carboxylic acid (*S*)-**65** (36 mg, 0.2 mmol, 1 eq) in dry dichloromethane (2 mL), oxalyl chloride (34 µL, 0.4 mmol, 2 eq) is added followed by a drop of dry DMF at 0°C. The mixture is allowed to warm up to room temperature and stirred for a total of 2 hours. Afterwards, the mixture is concentrated under high vacuum and the resultant residue is dissolved in dry dichloromethane (1 mL). A solution of L-phenylalanine ethyl ester (77 mg, 0.4 mmol, 2 eq) in dry dichloromethane (1 mL) is added drop-wise to the mixture mixture. Following that, triethylamine (70 µL, 0.5 mmol, 2.5 eq) is added and the resultant mixture is stirred for 2 hours at room temperature. The reaction mixture is concentrated in high vacuum and flash chromatography on silica gel (ethyl acetate/hexanes 1:9) results in the pure product (*S*,*S*)-**94** as a sticky waxy liquid (64 mg, 90%): TLC analysis (ethyl acetate/hexanes 1:9) R_f = 0.5; $[\alpha]_D^{20}$ = +32° (*c* = 1.0, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 7.36-7.18 (8H, m, aryl), 6.89-6.86 (2H, m, aryl), 5.58 (1H, t, *J* = 9.0 Hz, NH), 4.86-4.82 (1H, m, d), 4.13 (2H, q, *J* = 7.2 Hz, b), 3.03-2.96 (2H, m, e), 2.05-1.99 (2H, m, i), 1.50 (0.12H, s, h (minor diastereomer, 4%)), 1.46 (2.88H, s, h (major diastereomer, 96%)), 1.23 (3H, t, *J* = 7.2 Hz, a), 0.81 (2.89H, t, *J* = 7.2 Hz, j (major diastereomer, 96%)), 0.70 (0.11H, t, *J* = 7.2 Hz, j (minor diastereomer, 4%)) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 176.56 (f), 171.65 (c),

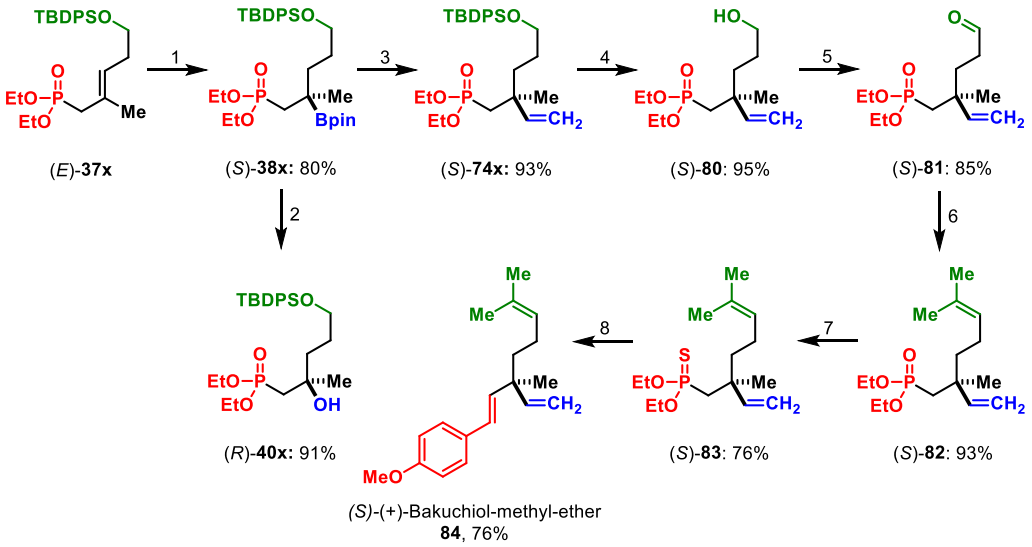
143.73 (aryl), 136.04 (aryl), 129.34 (aryl), 128.83 (aryl), 128.66 (aryl), 127.11 (aryl), 61.55 (b), 53.06 (d), 50.92 (g), 37.96 (e), 31.42 (i), 23.20 (h), 14.29 (a), 8.93 (j) ppm; IR (neat) 3359 (amide N-H), 2973 (aromatic C-H), 2879 (aliphatic C-H), 1735 (ester C=O), 1660 (amide C=O), 1495 (aromatic C=C), 1445 (aromatic C=C) cm^{-1}. The ^1H NMR analysis provided the dr to be 96:4.



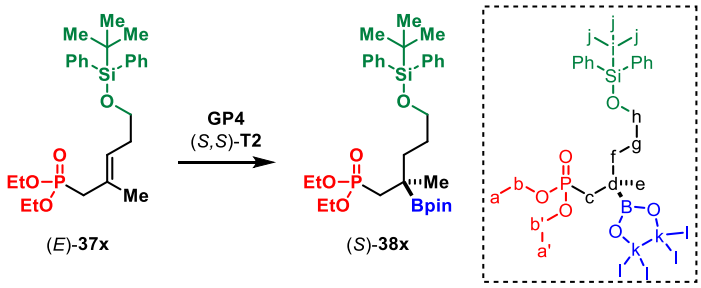
Synthesis of the aryl ketone (*S*)-**66:**[36] This transformation is carried out with some modifications of the original reported procedure[37] by Maeda et. al. as follows: To a suspension of magnesium turnings (11 mg, 0.46 mmol) in dry THF (1.5 mL) under a nitrogen atmosphere was added bromobenzene (47 µL, 0.45 mmol, 3 eq) and the resultant mixture was refluxed for a total of 2 hours until the solution turned brown and all of the magnesium dissolved. The resultant Grignard reagent is cooled down to room temperature and then to -78°C using a dry ice-acetone bath. A solution of acylphosphonate (*S*)-**61** (45 mg, 0.15 mmol, 1 eq) in dry THF (0.75 mL) is added to the reaction mixture and the resultant mixture is stirred at -78°C for 15 minutes. Following this, the reaction mixture is acidified to pH 1 using 1N HCl and the resultant mixture is extracted with dichloromethane (25 mL x 3). The combined organic extracts are dried over Na_2SO_4 and concentrated in vacuum. The resultant residue is dissolved in THF (1 mL) and a 2N solution of NaOH (0.5 mL) is added drop-wise. The resultant mixture is stirred for 1 hour. Afterwards, the mixture is extracted with diethyl ether (10 mL x 3) and the combined organics were washed with brine, dried over Na_2SO_4 and concentrated in vacuum to afford pure phenyl ketone (*S*)-**66** (28 mg, 78%): TLC analysis (ethyl acetate/hexanes 1:49) R_f = 0.5; $[\alpha]_D^{20}$ = +37° (*c* = 1.0,

C_6H_6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.21 (10H, m, aryl), 2.24-2.05 (2H, m, d), 1.58 (3H, s, c), 0.77 (3H, t, *J* = 7.4 Hz, e) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 204.00 (a), 144.56 (aryl), 137.15 (aryl), 131.72 (aryl), 129.63 (aryl), 129.08 (aryl), 128.10 (aryl), 126.95 (aryl), 126.48 (aryl), 55.16 (b), 32.27 (d), 23.92 (c), 8.83 (e) ppm; IR (neat) 3059 (aromatic C-H), 2971 (aliphatic C-H), 1674 (C=O), 1495 (aromatic C=C), 1445 (aromatic C=C), 1232, 907 cm^{-1}.

5.10. Total synthesis of (*S*)-(+)-Bakuchiol Methyl Ether

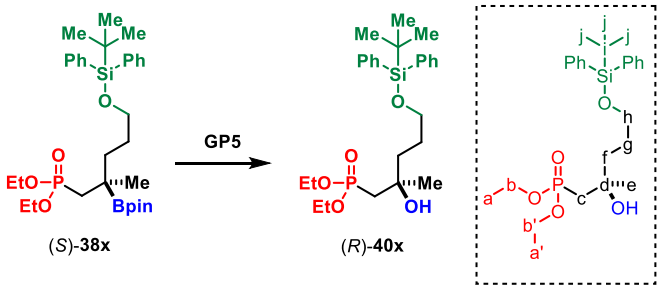


Step 1: CAHB of the trisubstituted alkene substrate (*E*)-**37x** with (*S,S*)-**T2** to prepare chiral tertiary boronic ester (*S*)-**38x**.

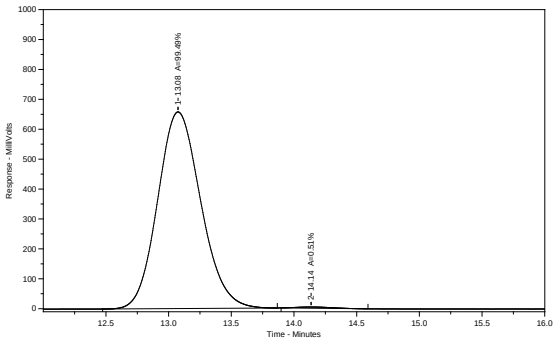
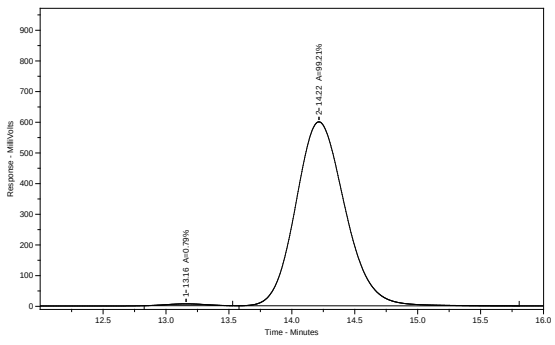


The trisubstituted alkene substrate (*E*)-**37x** (1.90 g, 4.00 mmol) is subjected to gram-scale CAHB with (*S*,*S*)-**T2** according to **GP4**. Flash chromatography of the hydroboration reaction mass on silica gel yields the tertiary boronic ester (*S*)-**38x** (1.93 g, 80%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 1:2) R_f = 0.6; $[\alpha]_D^{20}$ = +2.8° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz; $CDCl_3$) δ 7.66-7.64 (4H, m, aryl), 7.42-7.26 (6H, m, aryl), 4.07-4.03 (4H, m, b+b'), 3.61 (2H, t, *J* = 6.3 Hz, h), 2.04-1.95 (1H, m, c), 1.70-1.65 (1H, m, c), 1.60-1.47 (3H, m, f+g), 1.40-1.37 (1H, m, f), 1.31-1.28 (6H, m, a+a'), 1.24 (12H, s, l), 1.10 (3H, s, e), 1.03 (9H, s, j) ppm; ^{13}C NMR (175 MHz; $CDCl_3$) δ 135.57 (aryl), 134.10 (aryl), 129.50 (aryl), 127.71 (aryl), 127.58 (aryl), 83.44 (k), 64.59 (h), 61.13-60.86 (m, b+b'), 36.49 (g) , 36.39 (d), 34.29 (d, $^1J_{C\text{-}P}$ = 136.5 Hz, c), 28.51 (f), 26.87 (j), 24.92 (l), 21.88 (d, $^3J_{C\text{-}P}$ = 5.25 Hz, e), 19.24 (i), 16.52-16.47 (m, a+a') ppm; ^{11}B NMR (225 MHz, $CDCl_3$) δ 36.75 ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 32.34 ppm; IR (neat) 3071 (aromatic C-H), 2898 (aliphatic C-H), 2359, 2228, 1976, 1589, 1371 (C-O), 1214 (P=O), 1026, 955 cm^{-1}; HRMS (ESI) calculated for $C_{32}H_{52}BNaO_6PSi^+$ 625.3256, found 625.3271 *m/z*. Enantiomer ratio was determined by chiral HPLC analysis of the tertiary alcohol derivative **40x**.

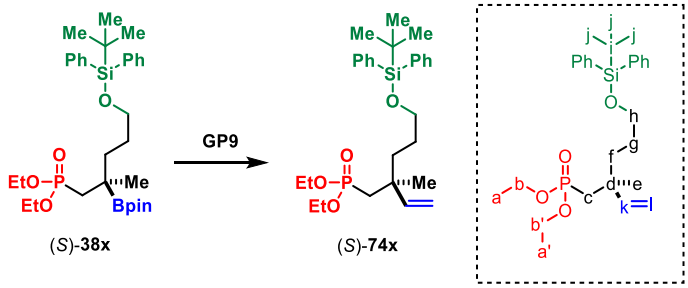
<u>Step 2:</u> Oxidation of chiral tertiary boronic ester (*S*)-**38x** to chiral tertiary alcohol (*R*)-**40x** to determine enantiomer ratio.



The tertiary boronic ester (*S*)-**38x** (60 mg, 0.10 mmol) is subjected to oxidation according to **GP5**. Workup of the reaction mass post oxidation yields the chiral tertiary alcohol (*R*)-**40x** (45 mg, 91%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 1:2) R_f = 0.4; $[\alpha]_D^{20}$ = +5.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.68 (4H, m, aryl), 7.46-7.38 (6H, m, aryl), 4.19-4.08 (4H, m, b+b'), 3.99 (1H, s, OH), 3.69 (2H, t, *J* = 5.6 Hz, h), 2.10-1.95 (2H, m, c), 1.73-1.63 (4H, m, f+g), 1.38-1.32 (9H, m, a+a'+e), 1.07 (9H, s, j) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.68 (aryl), 134.02 (aryl), 129.68 (aryl), 127.73 (aryl), 70.52 (d, $^2J_{C\text{-}P}$ = 5 Hz, d), 64.34 (h), 61.80-61.68 (m, b+b'), 40.01 (d, $^3J_{C\text{-}P}$ = 12 Hz, f), 37.48 (d, $^1J_{C\text{-}P}$ = 135 Hz, c), 28.10 (d, $^3J_{C\text{-}P}$ = 9 Hz, e), 27.48 (g), 26.98 (j), 19.32 (i), 16.51 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.08 ppm; IR (neat) 3245 (OH), 3070 (aromatic C-H), 2857 (aliphatic C-H), 1223 (P=O), 1051 (C-O), 1022 (C-O), 959, 701, 613 cm^{-1}; Enantiomer ratio was determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = isopropanol:hexanes 10:90; Flow rate = 0.75 mL/min; HPLC UV detector λ = 210 nm, rt. HPLC traces:

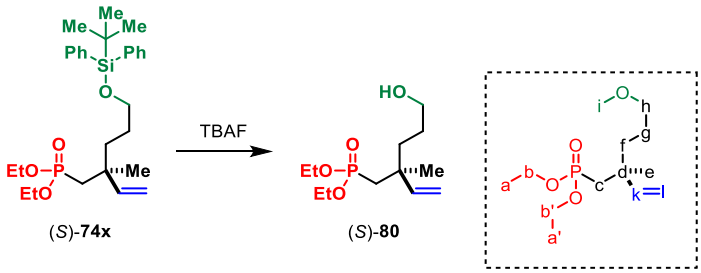
(a). R:S = 0.5:99.5; CAHB of **37x** with (*R*,*R*)-**T2**, then oxidation:	(b). R:S = 99.2:0.8; CAHB of **37x** with (*S*,*S*)-**T2**, then oxidation:
	

Step 3: Vinylation of chiral tertiary boronic ester (*S*)-**38x**.



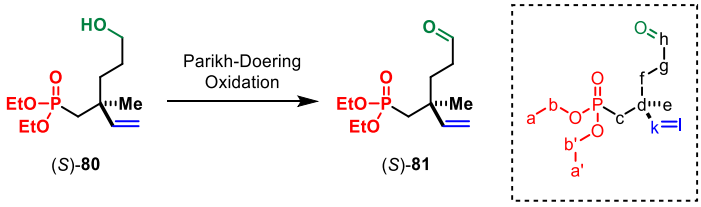
Following the general procedure for vinylation of chiral tertiary boronic esters (**GP9**), the chiral tertiary boronic ester (*S*)-**38x** (1.8 g, 3.0 mmol) yields the chiral vinyl phosphonate (*S*)-**74x** (1.4 g, 93%) as a colorless viscous oil: TLC analysis (ethyl-acetate/hexanes 1:1) $R_f = 0.5$; $[\alpha]_D^{20} = +1.1^o$ (*c* = 1.0, $CHCl_3$); ^1H NMR (700 MHz; $CDCl_3$) δ 7.68-7.67 (4H, m, aryl), 7.43-7.37 (6H, m, aryl), 5.85 (1H, dd, *J* = 11.2, 6.3 Hz, k), 5.04-4.97 (2H, m, l), 4.10-4.03 (4H, m, b+b'), 3.65 (2H, t, *J* = 6.3 Hz, h), 1.86 (2H, d, *J* = 18.9 Hz, c), 1.58-1.49 (4H, m, h+i), 1.31 (6H, t, *J* = 7 Hz, a+a'), 1.22 (3H, s, e), 1.07 (9H, s, j) ppm; ^{13}C NMR (175 MHz; $CDCl_3$) δ 146.06 (d, $^3J_{C\text{-}P}$ = 8.75 Hz, k), 135.57 (aryl), 134.01 (aryl), 129.55 (aryl), 127.62 (aryl), 111.89 (l), 64.31 (h), 61.25-61.08 (m, b+b'), 37.95 (d), 37.77 (d, $^3J_{C\text{-}P}$ = 10.5 Hz, f), 36.96 (d, $^1J_{C\text{-}P}$ = 138.25 Hz, c), 27.47 (g), 26.89 (j), 23.89 (d, $^3J_{C\text{-}P}$ = 5.25 Hz, e), 19.23 (i), 16.46 (d, $^3J_{C\text{-}P}$ = 7 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$)) δ 29.50 ppm; IR (neat) 2977 (aromatic C-H), 2859 (aliphatic C-H), 1589 (C=C), 1471, 1240 (P=O), 1026 (C-O), 730, 701, 613 cm^{-1}.

Step 4: Silyl ether deprotection of chiral vinyl posphonate (*S*)-**74x**.



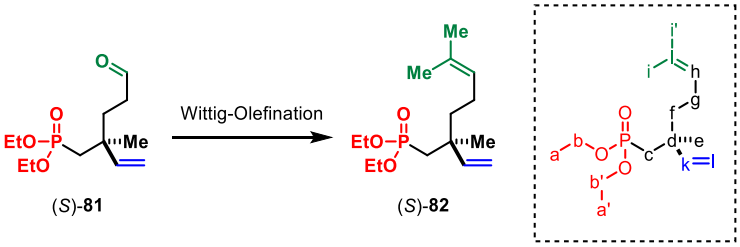
Tetrabutylammonium fluoride (TBAF; 1M solution in THF, 5 mL, 5 mmol, 2 equiv.) is added to a solution of (*S*)-**74x** (1.26 g, 2.50 mmol, 1.00 eq) in THF (25 mL) at 0 ºC. The reaction mixture is allowed to warm up to room temperature and stirred overnight. Afterwards, the reaction mass is concentrated in vacuum and is purified by flash chromatography on silica gel (methanol/ethyl-acetate 1:20) afforded the desired product (*S*)-**80** as a colorless viscous oil (630 mg, 2.38 mmol, 95%): TLC analysis (methanol/ethyl-acetate 1:20) R_f = 0.4; $[\alpha]_D^{20}$ = –1.23º (*c* = 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.78 (1H, dd, *J* = 10.5, 7 Hz, j), 4.96-4.90 (2H, m, k), 4.03-4.96 (4H, m, b+b'), 3.52 (2H, t, *J* = 6.3 Hz, h), 3.17 (1H, broad s, i), 1.84-1.76 (2H, m, c), 1.56-1.42 (4H, m, f+g), 1.24 (3H, t, *J* = 7 Hz, a+a'), 1.14 (3H, s, e); ^{13}C NMR (175 MHz, $CDCl_3$) δ 146.14 (d, $^3J_{C\text{-}P}$ = 10.5 Hz, j), 111.73 (k), 62.67 (h), 61.31-61.24 (m, b+b'), 37.86 (d, $^2J_{C\text{-}P}$ = 1.75 Hz, d), 37.17 (d, $^3J_{C\text{-}P}$ = 8.75 Hz, f), 36.14 (d, $^1J_{C\text{-}P}$ = 138.25 Hz, c), 27.43 (g), 24.48 (d, $^3J_{C\text{-}P}$ = 5.25 Hz, e), 16.35 (d, $^3J_{C\text{-}P}$ = 7 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.48 ppm; IR (neat) 3379 (O-H), 2979 (C-H), 1740, 1638, 1224 (P=O), 1026, 1024, 951, 831, 703, 607 cm^{-1}; HRMS (ESI) calculated for $C_{12}H_{25}NaO_4P^+$ 287.1383, found 287.1385 *m/z*.

Step 5: Parikh-Doering oxidation[38] of alcohol (*S*)-**80** to yield phosphono-aldehyde (*S*)-**81**.



DMSO (0.80 mL, 14 mmol, 5.0 eq), Hunig's base (1.57 mL, 9.08 mmol, 4.00 eq) and sulfur trioxide pyridine complex (750 mg, 4.76 mmol, 2.10 eq) are added sequentially to a solution of the alcohol (*S*)-**80** (600 mg, 2.27 mmol, 1.00 eq) in dry CH_2Cl_2 (20 mL) at 0 ^oC. The resulting solution is allowed to warm up to room temperature and stirred for a total of 3 hours. Afterwards, the reaction is quenched with brine (10 mL) and the organic layer separated. The aqueous layer is extracted with EtOAc (20 mL x 3) and the combined organic layers are concentrated under reduced pressure. The concentrate is purified by flash chromatography on silica gel (ethyl acetate) to yield the final product (*S*)-**81** as a colorless oil (507 mg, 1.93 mmol, 85%): TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = –2.9^o (*c* = 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (1H, s, h), 5.79 (1H, dd, *J* = 10.8, 6.6 Hz, j), 5.08-4.95 (2H, m, k), 4.12-4.00 (4H, m, b+b'), 2.38 (2H, m, g), 1.95-1.76 (4H, m, c+h), 1.32-1.27 (6H, m, a+a'), 1.21 (3H, s, e) ppm;^{13}C NMR (75 MHz, $CDCl_3$) δ 202.23 (h), 145.21 (d, $^3J_{C\text{-}P}$ = 10.5 Hz, j), 112.88 (k), 61.43-61.26 (m, b+b'), 39.48 (g), 37.74 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 36.57 (d, $^1J_{C\text{-}P}$ = 138.75 Hz, c), 32.72 (d, $^3J_{C\text{-}P}$ = 9 Hz, f), 23.95 (d, $^3J_{C\text{-}P}$ = 6 Hz, e), 16.41 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.76 ppm; IR (neat) 2981 (aliphatic C-H), 2722 (sp^2 C-H), 1722 (C=O), 1637, 1238 (P=O), 1023, 955, 831, 781 cm^{-1}.

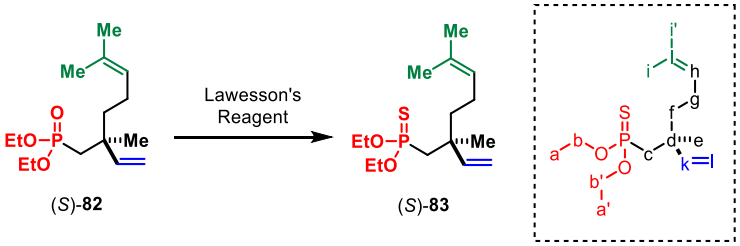
Step 6: Wittig olefination of aldehyde (*S*)-**81** to form the diene intermediate (*S*)-**82**.



A 2.5 *M* solution of *n*BuLi in hexanes (0.87 mL, 2.18 mmol, 1.30 eq) is added dropwise to a stirred suspension of isopropyltriphenylphosphonium iodide (1.00 g, 2.35 mmol, 1.40 eq) in dry THF (16 mL) at 0°C. The resulting orange-brown solution is allowed to stir for 1 hour at room temperature and then the reaction mixture is cooled to –78°C using a dry ice-acetone bath. A solution of the aldehyde (*S*)-**81** (400 mg, 1.52 mmol, 1.00 eq) in THF (8 mL) is added dropwise to the reaction mixture and the resultant mass is allowed to warm up to room temperature and stirred for a total of 24 hours. The reaction is quenched with 10 mL of saturated ammonium chloride solution and the phases are separated. The aqueous phase is extracted twice with 20 mL portions of ethyl acetate. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuum. Flash chromatography on silica gel (ethyl-acetate/hexanes 1:1) yields the pure product (*S*)-**82** (408 mg, 1.42 mmol, 93%) as a colorless oil: TLC analysis (ethyl-acetate/hexanes 1:1) R_f = 0.5; $[\alpha]_D^{20}$ = +8.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (1H, dd, *J* = 10.83, 6.6 Hz, j), 5.09-4.94 (3H, m, k+h), 4.12-4.00 (4H, m, b+b'), 1.92-1.82 (4H, m, c+g), 1.65 (3H, s, i'), 1.57 (3H, s, i), 1.52-1.45 (2H, m, f), 1.32-1.28 (6H, t, *J* = 7.05, a+a'), 1.21 (3H, s, e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.10 (d, $^3J_{C\text{-}P}$ = 9.75 Hz, j), 131.12 (l), 124.41 (h), 111.78 (k), 61.25-61.06 (m, b+b'), 41.69 (d, $^3J_{C\text{-}P}$ = 10.5 Hz, f), 38.18 (d, $^2J_{C\text{-}P}$ = 3 Hz, d), 36.68 (d, $^1J_{C\text{-}P}$ = 137.25 Hz, c), 25.67 (i'), 23.85 (d, $^3J_{C\text{-}P}$ = 6 Hz, e), 22.92 (g), 17.62 (i), 16.41 (d, $^3J_{C\text{-}P}$ = 6 Hz, a+a') ppm; ^{31}P NMR (121 MHz) δ 29.71 ppm; IR (neat)

2977 (sp^2 C-H), 2909 (sp^3 C-H), 1660 (C=C), 1243 (P=O), 1024, 954, 828 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{29}NaO_3P^+$ 311.1747, found 311.1755 *m/z*.

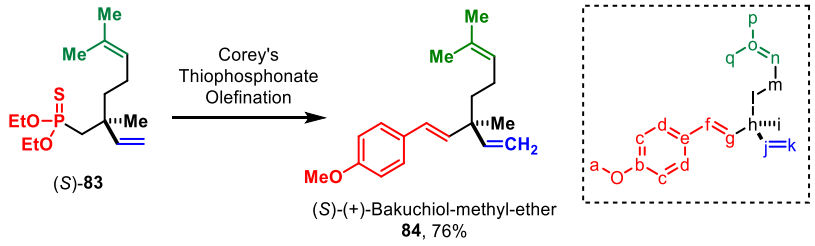
Step 7: Thionylation of the phosphonate (*S*)-**82** using Lawesson's reagent[39] to yield thiophosphonate (*S*)-**83**.



A mixture of phosphonate functionalized chiral diene (*S*)-**82** (87 mg, 0.30 mmol, 1.0 eq) and Lawesson's reagent (242 mg, 0.60 mmol, 2.0 eq) in dry toluene (3 mL) is heated at reflux for 6 hours. The solution turns homogenous after heat is applied. At this point, ^{31}P-NMR analysis of the crude reaction mixture showed the disappearance of the phosphonate starting material peak at ~30 ppm and the appearance of a new peak at ~95 ppm which corresponds to the thiophosphonate product. The mixture is cooled to room temperature and filtered over a bed of celite to get rid of insoluble materials and the combined filtrates are concentrated under reduced pressure. Flash chromatography on silica gel (ethyl-acetate/hexanes 1:50) yields the chiral thiophosphonate (*S*)-**83** as a light yellow oil (69 mg, 76%): TLC analysis (ethyl-acetate.hexanes 1:50) R_f = 0.5; $[\alpha]_D^{20}$ = +5.1° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (1H, dd, *J* = 10.8, 6.6 Hz, j), 5.11-4.95 (3H, m, k+h), 4.22-4.00 (4H, m, b+b'), 2.17 (2H, d, *J* = 16.2 Hz, c), 1.99-1.88 (2H, m, g), 1.69 (3H, s, i'), 1.60 (3H, s, i), 1.57-1.48 (2H, m, f), 1.31 (6H, t, *J* = 7.1 Hz, a+a'), 1.26 (3H, s, e) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.29 (d, $^3J_{C\text{-}P}$ = 9 Hz, j), 131.51 (l), 124.55 (h), 111.78 (k),

62.13 (dd, $^{2}J_{C\text{-}P}$ = 7.5, 6.75 Hz, b+b'), 45.40 (d, $^{1}J_{C\text{-}P}$ = 108.75 Hz, c), 41.87 (d, $^{3}J_{C\text{-}P}$ = 9.75 Hz, f), 39.26 (d, $^{2}J_{C\text{-}P}$ = 3.75 Hz, d), 25.81 (i'), 23.89 (d, $^{3}J_{C\text{-}P}$ = 6 Hz, e), 22.86 (g), 17.68 (i), 16.16 (d, $^{3}J_{C\text{-}P}$ = 6.75 Hz, a+a') ppm; ^{31}P NMR (121 MHz) δ 95.29 ppm; IR (neat) 3082 (sp^2 C-H), 2976 (sp^3 C-H), 1638, 1443, 1261, 1024 (P-O), 950 (P-O), 650 (P=S) cm^{-1}.

Step 8: Alkene synthesis from the α-lithiothionophosphonate ester: Synthesis of bakuchiol methyl ether.



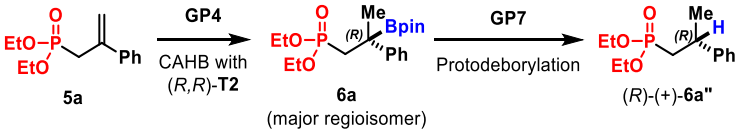
This transformation is carried out with some modifications of the original procedure[40] described by E. J. Corey et. al. as follows: A solution of *n*BuLi in hexanes (1.6M solution in hexanes; 0.2 mL, 0.315 mmol, 2.1 eq) is added dropwise to a solution of the thiophosphonate (*S*)-**83** (46 mg, 0.15 mmol) in dry tetrahydrofuran (1.5 mL) under nitrogen at –78°C. The cooling bath is removed, and the mixture is allowed to warm to room temperature and stirred for 1 hour. The mixture is re-cooled to –78°C and 4-methoxy-benzaldehyde (40 μL, 0.33 mmol, 2.2 eq) is added dropwise to the reaction mixture. The mixture is stirred at –78°C for 30 minutes and then allowed to warm up to room temperature and stirred for a total of 9 hours. The reaction is quenched with the addition of saturated aq. NH_4Cl and is extracted with diethyl ether (5 mL x 3). The combined organics are washed with brine, dried over Na_2SO_4 and concentrated in vacuum. Flash chromatography on silica gel (ethyl-acetate/hexanes 1:50) yields the desired product (*S*)-**84** as a light yellow

oil (31 mg, 77%): TLC analysis (ethyl-acetate/hexanes 1:50) R_f = 0.5; $[\alpha]_D^{20}$ = +19.1° (*c* = 1.0, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.7 Hz, d), 6.84 (2H, d, *J* = 8.7 Hz, c), 6.26 (1H, d, *J* = 16.4 Hz, f), 6.07 (1H, d, *J* = 16.4 Hz, g), 5.88 (1H, dd, *J* = 17.5, 10.5 Hz, j), 5.11 (1H, t, *J* = 7 Hz, n), 5.04-5.00 (2H, m, k), 3.80 (3H, s, a), 1.96 (2H, dt, *J* = 8.4, 7.7 Hz, m), 1.68 (3H, s, q), 1.58 (3H, s, p), 1.51-1.48 (2H, m, l), 1.20 (3H, s, i) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 158.88 (b), 146.15 (j), 135.95 (g), 131.45 (e), 130.85 (o), 127.30 (d), 126.67 (f), 124.96 (n), 114.05 (c), 112.00 (k), 55.45 (a), 42.68 (h), 41.45 (l), 25.85 (q), 23.50 (e), 23.38 (m), 17.78 (p) ppm; IR (neat) 2961 (sp^2 C-H), 2857 (sp^3 C-H), 1607 (C=C), 1510, 1455, 1247, 1173, 1034, 970, 910, 815, 732 cm^{-1}.

5.11. Absolute Configuration Assignments

5.11.1 CAHB of conjugated methylidene substrate 5a

5.11.1.1 Absolute configuration assignment of the major regioisomer: tertiary boronic ester 6a:

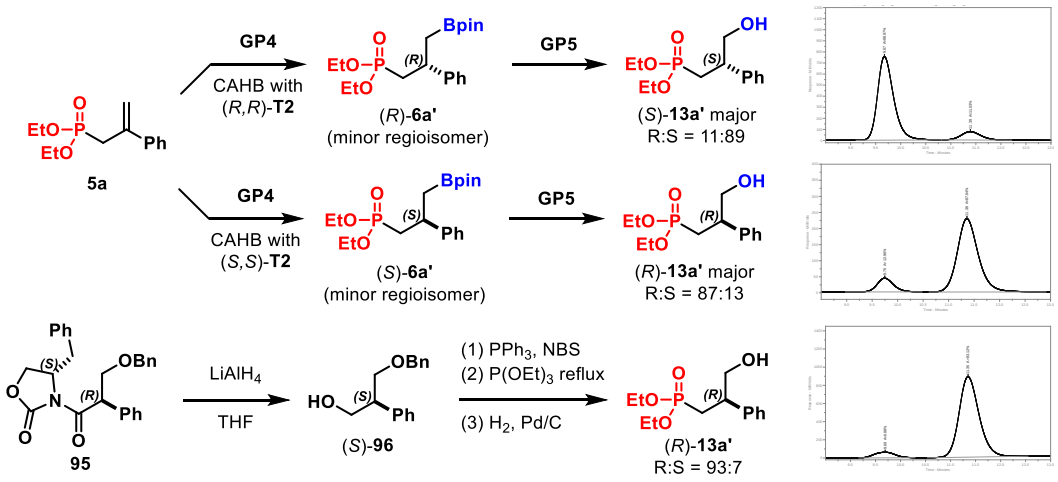


The configurations of all other chiral tertiary benzylic boronic esters derived from conjugated methylidene substrates are assigned based on the following. CAHB of phenyl-substituted methylidene substrate **5a** with (*R*,*R*)-**T2** results in the formation of chiral tertiary benzylic boronic ester **6a** as the major product. The latter is protodeboronated to **6a"** (see **GP7**) using conditions reported by Aggarwal[8] giving the corresponding chiral reduced product whose configuration is assigned *"R"* based on the positive value of its optical rotation for this previously reported compound.[41] Since protodeboronation of chiral

tertiary benzylic boronic esters proceeds with retention of stereochemistry, the chiral boronic ester **6a** derived from CAHB with (*R,R*)-**T2** is assigned as *"R"*, the result of B-H addition to the *top-face* of the alkene in the perspective drawn.

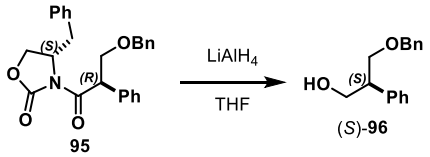
The assigned absolute configuration is further supported by conversion of (*R*)-**6a** to (*S*)-**57** setting the all-carbon quaternary carbon stereocenter with retention of stereochemistry; the details are described above. [Note: Aggarwal[11] has shown that chiral tertiary boronic esters undergo vinylation reaction with stereoretention]. Hydrogenation to (*S*)-**58** sets the stage for conversions to the known alcohol (*S*)-(+)-**62**, carboxylic acid (*S*)-(+)-**65**, and ketone (*S*)-(+)-**66**, each of which gives the expected (+) sign of optical rotation. However, the literature indicates that aldehyde (*S*)-**60** and amide (*S*)-**64** should have the (-) sign of rotation which we believe is incorrect. We find (+)-rotations for each, and furthermore, $NaBH_4$ reduction of our (+)-**60** affords (*S*)-(+)-**62**.

5.11.1.2 Absolute configuration assignment of minor regioisomer: primary boronic ester 6a':



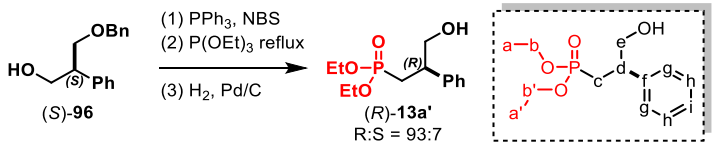
CAHB of the conjugated methylidene substrate **5a** also gives a small amount of the chiral primary boronic ester **6a'** as a minor product. For mechanistic interest and to compare to other directed-CAHBs, we proved the stereochemistry of the major enantiomer of **6a'** that is formed. Oxidation of **6a'** resulted in the formation of chiral γ-hydroxy phosphonate **13a'**; (*R*,*R*)-**T2** gives the S-isomer and (*S*,*S*)-**T2** gives the R-isomer. To establish those assignments, (*R*)-**13a'** was synthesized using the Evans' chiral auxiliary for asymmetric alkylation to establish the stereochemistry. The oxazolidinone derivative **95** was prepared according to literature procedure.[42] Reduction of the oxazolidinone derivative **95** using $LiAlH_4$ in THF afforded the chiral alcohol (*S*)-**96**; the negative value of its optical rotation confirms the absolute configuration.[18] Sequential bromination (PPh_3/NBS), Michaelis-Arbuzov rearrangement (**GP1**) and benzyl-ether cleavage (H_2/Pd-C) afforded the enantiopure chiral γ-hydroxy phosphonate (*R*)-**13a'**. As illustrated above, analysis of the chiral HPLC traces and optical rotations revealed that the chiral γ-hydroxy phosphonate (*R*)-**13a'** obtained via asymmetric alkylation is the enantiomer of the minor product obtained from CAHB of **5a** using (*R*,*R*)-**T2** followed by oxidation. (*S*)-**13a'** arises from the B-H addition to the *"top-face"* of the alkene **5a** in the perspective drawn.

Characterization Data:



To a solution of oxazolidinone derivative **95** (623 mg, 1.50 mmol, 1.00 eq) in dry THF (15 mL) at 0^oC is added $LiAlH_4$ (230 mg, 6.00 mmol, 4.00 eq) slowly and the resultant mixture stirred vigorously for 1 hour. Afterwards, the reaction mixture is carefully quenched with the addition of ethyl acetate (20 mL) and water (2 mL) and the resultant mixture was

filtered over a small pad of silica gel and the silica pad was washed with ethyl acetate (20 mL). The combined filtrates are concentrated under reduced pressure. Flash chromatography over silica gel (ethyl acetate/hexanes 1:3) affords the alcohol (*S*)-**96** (309 mg, 85%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 1:3) R_f = 0.5; $[\alpha]_D^{20}$ = -35° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (10H, m), 4.59 (2H, s), 4.07-4.02 (1H, m), 3.93-3.79 (3H, m), 3.28-3.22 (1H, m), 2.47 (1H, br d, *J* = 9.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.77, 138.05, 128.86, 128.69, 128.20, 127.99, 127.87, 127.28, 73.88, 73.66, 66.75, 48.01 ppm; IR (neat) 3396 (O-H), 3028 (sp^2 C-H), 2863 (sp^3 C-H), 1495 (aromatic C=C), 1452 (aromatic C=C), 1363, 1075 (C-O), 1027 (C-O), 735, 696 cm^{-1}.

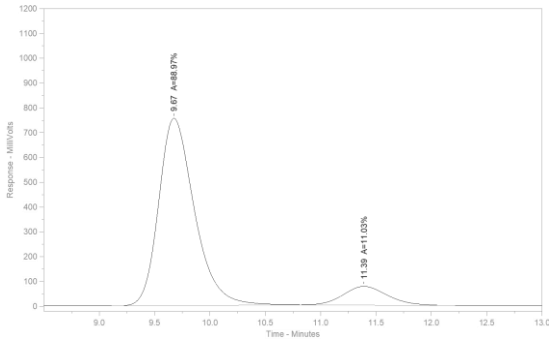
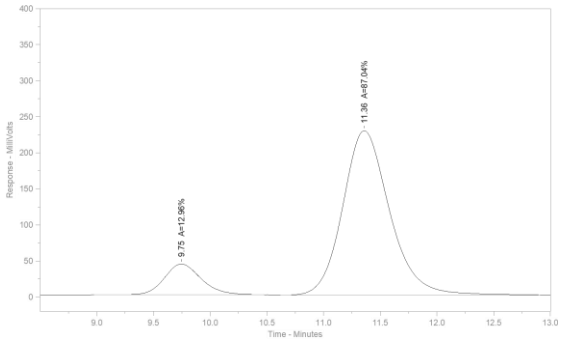
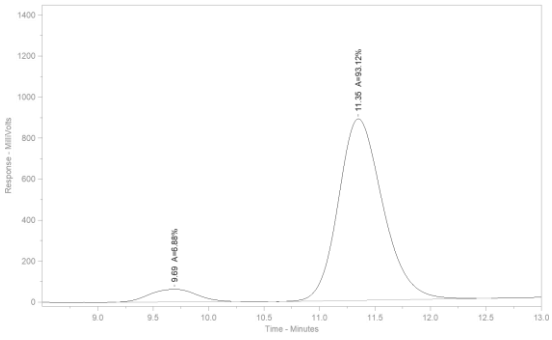


To a solution of the alcohol (*S*)-**96** (242 mg, 1.00 mmol, 1.00 eq) in dry dichloromethane (10 mL) at 0°C is added PPh_3 (393 mg, 1.50 mmol, 1.5 eq) and NBS (267 mg, 1.50 mmol, 1.5 eq). The resultant mixture is stirred for 1 hour when TLC (ethyl acetate/hexanes 1:3) indicates complete consumption of starting material. The solvent is evaporated under reduced pressure and 20% ethyl acetate in hexanes is added to the residue. The resultant mixture was filtered over a small bed of silica gel and the bed was further washed with more 20% ethyl acetate in hexanes (40 mL total). The combined filtrates were concentrated under reduced pressure. The resultant residue was refluxed with triethylphosphite (0.51 mL) under a nitrogen atmosphere for 6 hours. Following the Arbuzov rearrangement (crude NMR analysis: appearance of a phosphonate peak at ~31 ppm), excess triethylphosphite was distilled off using bulb-to-bulb distillation. A mixture of the resultant residue and 10%

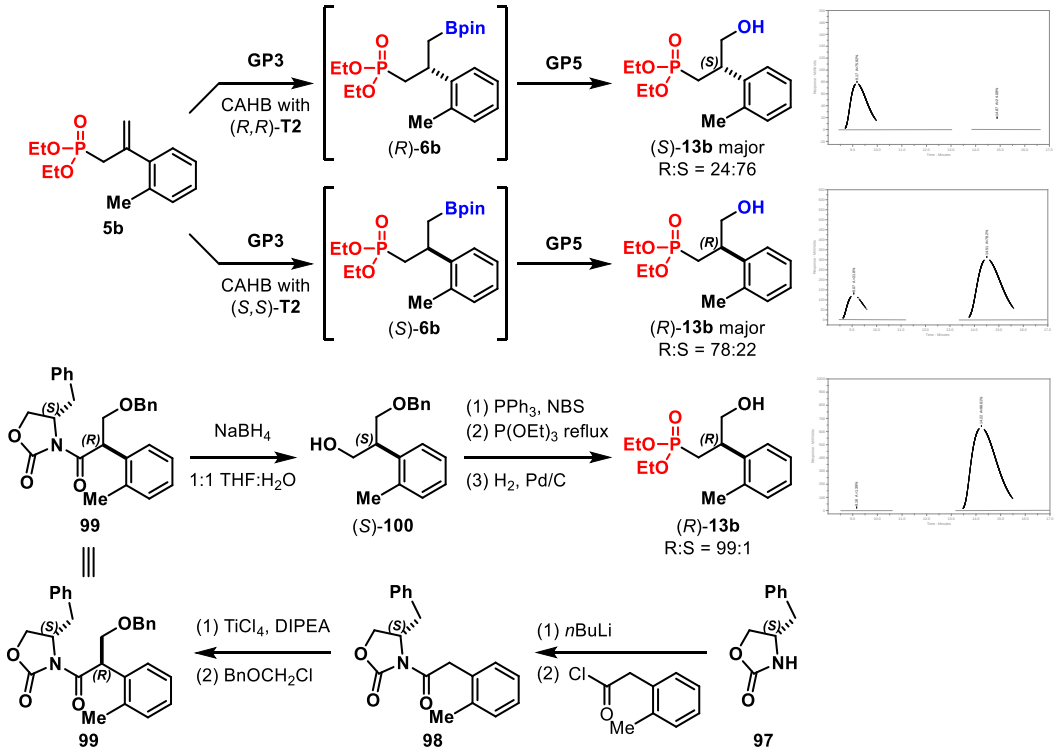
Pd on activated carbon (40 mg, 4.0 mol% Pd-loading) in ethanol (10 mL) is stirred under a hydrogen atmosphere (balloon pressure) for 6 hours. Afterwards, the mixture is filtered and concentrated under reduced pressure. Flash chromatography over silica gel (ethyl acetate/methanol 24:1) affords the phosphonate (*R*)-**13a'** as a colorless viscous oil (169 mg, 62% overall): TLC analysis (ethyl acetate/methanol 24:1) R_f = 0.5; $[\alpha]_D^{20}$ = -22° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (5H, m, aryl), 4.06-3.88 (4H, m, b+b'), 3.82-3.73 (2H, m, e), 3.48 (1H, br s, OH), 3.27-3.18 (1H, m, d), 2.38-2.28 (1H, m, c(1H)), 2.14-2.00 (1H, m, c(1H)), 1.23 (3H, t, *J* = 7.0 Hz, a or a'), 1.21 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.34 (d, $^3J_{C\text{-}P}$ = 11 Hz, f), 128.75 (g or h), 127.73 (g or h), 127.10 (i), 67.65 (d, $^3J_{C\text{-}P}$ = 10.25 Hz, e), 61.91 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.79 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 43.12 (d, $^2J_{C\text{-}P}$ = 3.0 Hz, d), 29.36 (d, $^1J_{C\text{-}P}$ = 140 Hz, c), 16.42 (d, $^3J_{C\text{-}P}$ = 6.0 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.38 ppm; IR (neat) 3372 (O-H), 2981 (sp^2 C-H), 2906 (sp^3 C-H), 1453 (aromatic C=C), 1391 (aromatic C=C), 1222 (P=O), 1051 (C-O), 1019 (C-O), 957 (P-O), 699 cm^{-1}.

Obtaining γ-hydroxyphosphonate 13a' from alkene substrate 5a: Substrate **5a** (1.02 g, 4.00 mmol) is subjected to CAHB according to **GP4**. After purification of the major product (tertiary boronic ester **6a**), the minor regioisomer **6a'** and the reduced product **6a''** are flushed out of the silica packed column with methanol, the mixture is concentrated under reduced pressure and is subjected to oxidation following **GP5**. Afterwards, the mixture is extracted with ethyl acetate (20 mL x 5) and the combined extracts are concentrated under reduced pressure. Flash chromatography over silica gel (ethyl acetate/methanol 24:1) affords the hydroxy phosphonate **13a'** as a colorless viscous oil (109 mg, 10% overall from the hydroboration/oxidation sequence). Enantiomer ratio is

determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AD; Mobile Phase = 90:10 Hexanes:Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a) R:S = 11:89, CAHB of **5a** with (*R*,*R*)-**T2** to form (*R*)-**6a'**, then oxidation to yield **13a'**: 	(b) R:S = 87:13, CAHB of **5a** with (*S*,*S*)-**T2** to form (*S*)-**6a'**, then oxidation to yield **13a'**: 
(c) R:S = 93:7, **13a'** (enriched with *"R"* enantiomer) obtained via chiral auxiliary sequence. 	

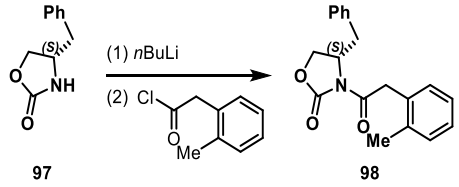
5.11.2 CAHB of conjugated methylidene substrate 5b bearing an *ortho*-methylphenyl group:



CAHB of conjugated methylidene substrate **5b** bearing an *ortho*-methyl phenyl group at the beta position resulted in an inseparable mixture of primary boronic ester **6b** (major product) along with the reduction side product. Oxidation of this CAHB mixture after partial purification (ref. **GP5**) allowed for the separation of the chiral γ-hydroxy phosphonate **13b** from other products. (*R*)-**13b** was independently synthesized via asymmetric alkylation using the Evans' chiral auxiliary to set the required stereochemistry. The chiral oxazolidinone auxiliary (*S*)-**97** (derived from L-phenylalanine) was treated with *n*BuLi, followed by 2-(o-tolyl)acetyl chloride to obtain intermediate **98**. Alkylation of **98** with benzyl-chloromethyl ether under standard conditions affords the oxazolidinone derivative **99**. Reduction of the oxazolidinone derivative **99** using $NaBH_4$ results in the chiral alcohol (*S*)-**100**. Sequential bromination (PPh_3/NBS), Michaelis-Arbuzov Rearrangement ($P(OEt)_3$ reflux) and benzyl-ether cleavage (H_2/Pd-C) affords the enantiopure chiral primary alcohol (*R*)-**13b**. Chiral HPLC analysis and optical rotation

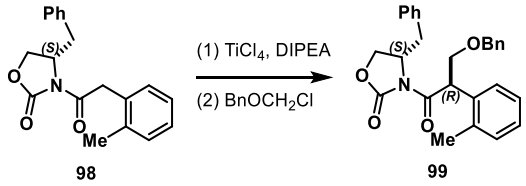
measurements show that (*R*)-**13b** obtained via asymmetric synthesis is the minor enantiomer obtained via CAHB of **5b** using (*R,R*)-**T2** followed by oxidation. The latter (*i.e.,* (*S*)-**13b**) arise B-H addition to the *"top-face"* of the alkene **5b** in the perspective drawn. The absolute configuration of chiral primary boronic ester derived from *ortho*-methoxy substituted substrate **5c** is assigned based on analogy.

Characterization Data:



A solution of *n*BuLi in hexanes (2.5M; 4.0 mL, 10 mmol, 1.0 equiv.) is added dropwise to a solution of the oxazolidinone auxiliary (*S*)-**97** (1.77 g, 10.0 mmol, 1 eq) in THF (20 mL) at -78^{o}C. The resultant mixture was stirred for 30 minutes, following which, a solution of 2-(o-tolyl)acetyl chloride (1.68 g, 10.0 mmol, 1.00 mmol) in THF (10 mL) is added dropwise to the reaction mixture. The resultant mixture is stirred for 1 hour at -78^{o}C, warmed up to room temperature and stirred for an additional 1 hour and then quenched with the addition of saturated aqueous NH_4Cl. The resultant mixture is extracted with ethyl acetate (20 mL x 3) and the combined organics are washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuum. Flash chromatography on silica gel (dichloromethane/ethyl-acetate/hexanes 1:2:17) affords the desired oxazolidinone derivative **98** as a light yellow solid (2.56 g, 83%): TLC analysis (ethyl acetate/hexanes 1:4) R_f = 0.5; $[\alpha]_D^{20}$ = +68^{o} (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (9H, m), 4.76-4.70 (1H, m), 4.42-4.22 (4H, m), 3.36 (1H, dd, *J* = 13.0, 3.0 Hz), 2.82 (1H, dd, *J* = 13.0, 10.0 Hz), 2.35 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.14, 153.75, 137.28,

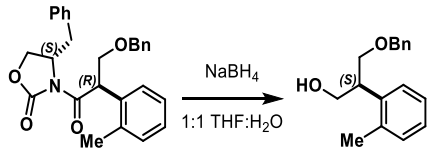
135.38, 132.55, 130.54, 130.37, 129.57, 129.13, 127.71, 127.53, 126.29, 66.47, 55.62, 40.11, 38.04, 19.81 ppm; IR (neat) 3060 (sp^2 C-H), 2921 (sp^3 C-H), 1771 (C=O), 1697 (C=O), 1387, 1357, 1249, 1210, 1104, 741, 695 cm^{-1}.



98 99

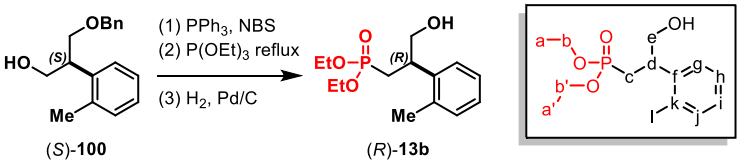
A 1M solution of $TiCl_4$ in dichloromethane (6.00 mL, 6.00 mmol, 1.50 equiv.) is added drop-wise to a solution of the oxazolidinone derivative **98** (1.24 g, 4.00 mmol, 1.00 mmol) in dry dichloromethane (8 mL) at 0°C. Diisopropylamine (1.4 mL, 8.0 mmol, 2.0 equiv.) is added to the resultant solution and the dark blue solution was stirred for 1 hour at 0°C. Following this, benzyl chloromethyl ether (1.14 mL, 8.00 mmol, 2.00 eq) is added dropwise and the resultant mixture is stirred at room temperature for 12 hours. (Note: Commercial benzylchloromethyl ether is contaminated with ~25% benzyl chloride, which can be removed via Kugelrohr distillation at 2 mmHg vacuum at 60°C. After distillation of benzyl chloride, about 90% clean benzyl chloromethyl ether is obtained which is contaminated with ~10% of formaldehyde dibenzyl acetal: this is used for synthesis). Afterwards, saturated aqueous NH_4Cl is added to quench the reaction and the resultant mixture is extracted with ethyl acetate (25 mL x 3). The combined organics are washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Flash chromatography over silica gel (ethyl acetate/hexanes 15:85) affords **99** as a viscous light-yellow liquid (1.39 g, 81%): TLC analysis (ethyl acetate/hexanes 1:3) R_f = 0.6; $[\alpha]_D^{20}$ = +220° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.14 (14 H, m), 5.61-5.57 (1H, m), 4.74-4.59 (3H, m), 4.19-4.09 (3H, m), 3.59-3.55 (1H, m), 3.37-3.33 (1H, m), 2.96-2.90

(1H, m), 2.49 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.72, 152.97, 138.39, 137.95, 135.41, 133.43, 131.14, 129.78, 129.12, 128.57, 127.86, 127.82, 127.51, 126.70, 126.29, 73.46, 71.65, 65.92, 55.82, 46.76, 37.91, 19.64 ppm; IR (neat) 3063 (sp^2 C-H), 2941 (sp^3 C-H), 1769 (C=O), 1691 (C=O), 1391, 1357, 1212, 1099, 743, 6951 cm^{-1}.



99 (*S*)-**100**

The oxazolidinone derivative **99** is cleaved to afford the chiral alcohol (*S*)-**100** according to literature procedure as follows: A solution of oxazolidinone **99** (859 mg, 2.00 mmol, 1.00 eq) in 1:1 THF: H_2O mixture (40 mL) is cooled in an ice-bath to 0^{o}C. To this, $NaBH_4$ (302 mg, 8.00 mmol, 4.00 eq) is added portion-wise and the resultant mixture is stirred vigorously for 9 hours. Afterwards, the reaction mixture is cooled down to 0^{o}C and was quenched with saturated aqueous NH_4Cl (Caution: careful addition is required, quenching is exothermic). The resultant mixture is extracted with ethyl acetate (3 x 30 mL) and the combined organics are washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash chromatography over silica gel (ethyl acetate/hexanes 1:3) affords the alcohol (*S*)-**100** as a colorless liquid (456 mg, 89%): TLC analysis (ethyl acetate/hexanes 1:3) R_f = 0.5; $[\alpha]_D^{20}$ = -25^o (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.31 (5H, m), 7.22-7.12 (4H, m), 4.60 (2H, s), 4.08-4.00 (1H, m), 3.92-3.82 (2H, m), 3.76 (1H, dd, *J* = 9.0, 4.5 Hz), 3.57-3.50 (1H, m), 2.62 (1H, br s), 2.40 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.01, 137.76, 136.65, 130.89, 128.71, 128.02, 127.87, 126.99, 126.42, 74.05, 73.69, 66.66, 43.08, 19.87 ppm; IR (neat) 3425 (O-H), 3027 (sp^2 C-H), 2861 (sp^3 C-H), 1493, 1453, 1362, 1093, 1067, 1027, 727, 696 cm^{-1}.



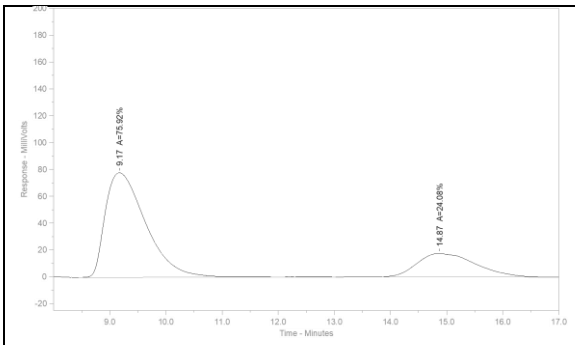
(*S*)-**100** (*R*)-**13b**

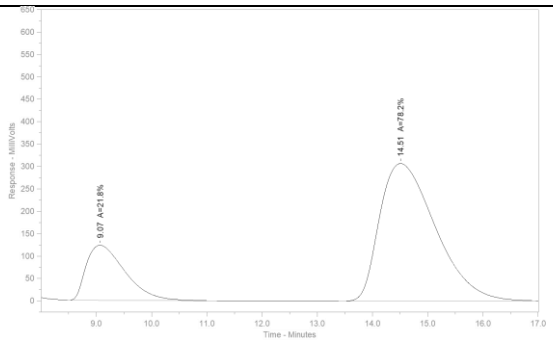
To a solution of the alcohol (*S*)-**100** (256 mg, 1.00 mmol, 1.00 eq) in dry dichloromethane (10 mL) at 0°C is added PPh_3 (393 mg, 1.50 mmol, 1.5 eq) and NBS (267 mg, 1.50 mmol, 1.5 eq) sequentially. The resultant mixture is stirred for 1 hour when TLC (ethyl acetate/hexanes 1:3) indicated complete consumption of starting material. The solvent is evaporated under reduced pressure and 20% ethyl acetate in hexanes is added to the residue. The resultant mixture is filtered over a small bed of silica gel and the bed is further washed with more 20% ethyl acetate in hexanes (40 mL total). The combined filtrates are concentrated under reduced pressure. The resultant residue is refluxed with triethylphosphite (0.51 mL) under a nitrogen atmosphere for 6 hours. Following the Arbuzov rearrangement (crude NMR analysis: appearance of a phosphonate peak at ~31 ppm), excess triethylphosphite is distilled off via bulb-to-bulb distillation. A mixture of the resultant residue and 10% Pd on activated carbon (80 mg, 8.0 mol% Pd-loading) in ethanol (10 mL) is stirred under a hydrogen atmosphere (balloon pressure) for 12 hours. Afterwards, the mixture is filtered and concentrated under reduced pressure. Flash chromatography over silica gel (ethyl acetate/methanol 49:1) affords the phosphonate (*R*)-**13b** as a colorless viscous oil (146 mg, 51% overall): TLC analysis (ethyl acetate/methanol 49:1) R_f = 0.5; $[\alpha]_D^{20}$ = -16.9° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.13 (4H, m, aryl), 4.11-3.97 (4H, m, b+b'), 3.85-3.77 (2H, m, e), 3.60-3.50 (1H, m, d), 2.41 (3H, s, l), 2.29 (1H, ddd, *J* = 18.0, 15.0, 8.5 Hz, c(1H)), 2.09 (1H, ddd, *J* = 19.0, 18.0, 5.5 Hz, c(1H)), 1.28 (3H, t, *J* = 7.0 Hz, a or a'), 1.28 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.79 (d, $^3J_{C\text{-}P}$ = 12.0 Hz, f), 136.13 (k), 130.86 (aryl), 126.92 (aryl),

126.61 (aryl), 126.05 (aryl), 67.63 (d, $^{3}J_{C\text{-}P}$ = 8.0 Hz, e), 62.11 (d, $^{2}J_{C\text{-}P}$ = 7.0 Hz, b or b'), 62.01 (d, $^{2}J_{C\text{-}P}$ = 6.5 Hz, b or b'), 38.00 (d, $^{2}J_{C\text{-}P}$ = 3.0 Hz, d), 29.94 (d, $^{1}J_{C\text{-}P}$ = 139 Hz, c), 19.85 (l), 16.57 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a'), 16.54 (d, $^{3}J_{C\text{-}P}$ = 6.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.90 ppm; IR (neat) 3364 (O-H), 2980 (sp^2 C-H), 2914 (sp^3 C-H), 1456 (aromatic C=C), 1391 (aromatic C=C), 1218 (P=O), 1019 (C-O), 961 (P-O), 757 cm^{-1}. HRMS (ESI) calculated for $C_{14}H_{23}O_4P+Na^+$ = 309.1232, found 309.1228 *m/z*.

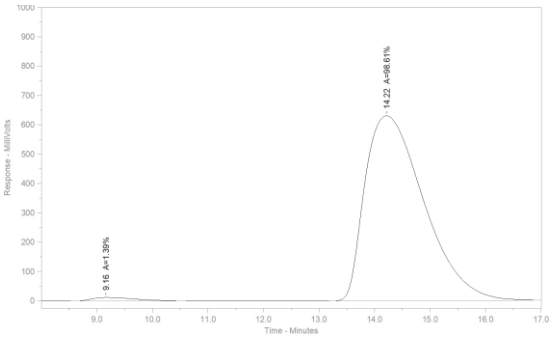
Obtaining γ-hydroxyphosphonate 13b from alkene substrate 5b: Following the general procedure for CAHB (**GP4**), the substrate **5b** (54 mg, 0.2 mmol) yields a mixture of boronic esters and reduced products that were not separable via silica gel chromatography. The crude CAHB mixture is chromatographed (ethyl acetate/hexanes 3:1) over silica gel to get rid of the non-polar colored complex and the polar metal residues. The crude mixture obtained after this partial purification is subjected to oxidation following **GP5** to obtain the γ-hydroxyphosphonate **13b** (47 mg, 82% overall from the hydroboration/oxidation sequence) as a colorless oil. Enantiomer ratio is determined by chiral HPLC analysis: Stationary phase = CHIRALPAK AS-H; Mobile Phase = 90:10 Hexanes:Isopropanol; Flow rate = 1.25 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

(a) R:S = 24:76, CAHB of **5b** with (*R*,*R*)-**T2**, followed by oxidation to yield (*S*)-**13b**:	(b) R:S = 78:22, CAHB of **5b** with (*S*,*S*)-**T2**, followed by oxidation to yield (*R*)-**13b**:

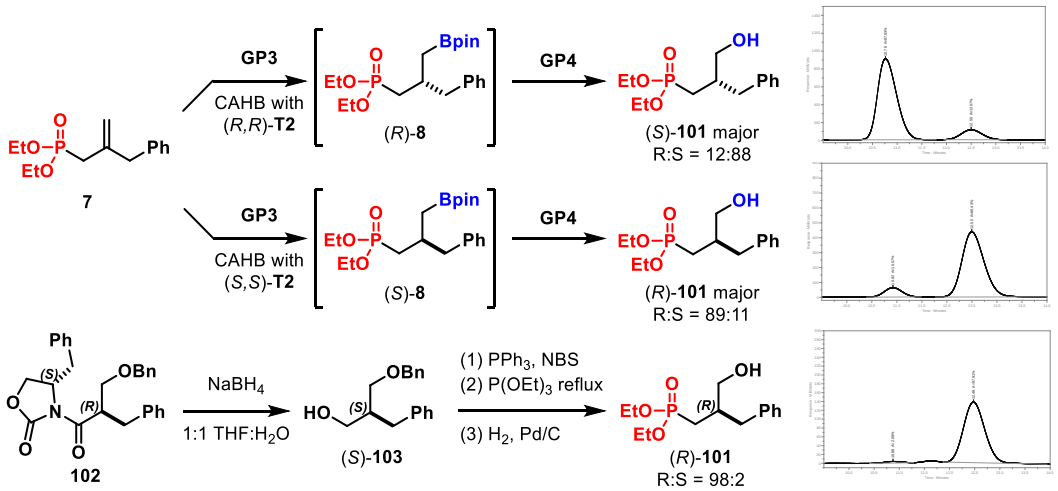




(c) R:S = 99:1, **13b** (enantioenriched *"R"*) obtained via chiral auxiliary sequence:

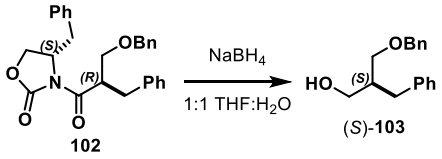


5.11.3 CAHB of non-conjugated methylidene substrate 7:



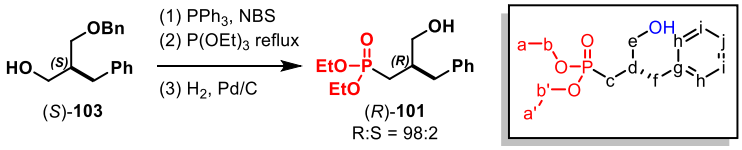
CAHB of the non-conjugated methylidene substrate **7** resulted in an inseparable mixture of primary boronic ester **8** (major product) along with the tertiary boronic ester **9** (minor product) along with some of the reduction product. Oxidation of the mixture after partial purification (ref. **GP5**) allowed for the separation of the chiral γ-hydroxy phosphonate **101** from the other products. (*R*)-**101** was independently synthesized via asymmetric alkylation using the Evans' chiral auxiliary. Oxazolidinone derivative **102** was prepared according to its literature report.[43] Reduction of the oxazolidinone derivative using $NaBH_4$ resulted in the chiral alcohol (*S*)-**103** whose absolute configuration was verified by the observed strong negative optical rotation.[44] Sequential bromination (PPh_3/NBS), Michaelis-Arbuzov rearrangement ($P(OEt)_3$ reflux) and benzyl-ether cleavage (H_2/Pd-C) affords primary alcohol (*R*)-**101**. Chiral HPLC analysis reveals that the product obtained via asymmetric synthesis and that of CAHB (using (*S,S*)-**T2**) and oxidation sequence from substrate **7** are enriched with the same configuration (*i.e., "R"*). The alcohol obtained from substrate **7** after CAHB (using (*R,R*)-**T2**) followed by oxidation is enriched with *"S"* configuration, which comes from the precursor boronic ester **8** enriched with the *"R"* configuration: which resulted from the B-H addition to the *"top-face"* of the alkene **7** in the perspective drawn.

Characterization Data:



The oxazolidinone derivative is cleaved to afford the chiral alcohol (*S*)-**103** according to the procedure outlined for the reduction of oxazolidinone derivative **100** in Sec. 5.11.2: The oxazolidinone derivative **102** (859 mg, 2.00 mmol, 1.00 eq) affords the chiral alcohol

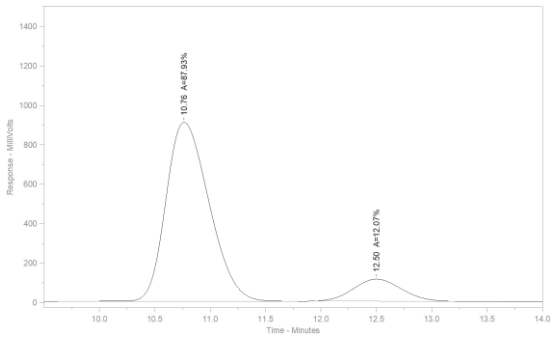
(*S*)-**103** (471 mg, 92%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 1:3) R_f = 0.5; $[\alpha]_D^{20}$ = -34.5° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.21 (10H, m), 4.54 (2H, dd, *J* = 18.0, 12.0 Hz), 3.80-3.62 (3H, m), 3.53 (1H, dd, *J* = 9.0, 6.5 Hz), 2.76-2.67 (2H, m), 2.61 (1H, t, *J* = 5.0 Hz), 2.23-2.16 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.15, 138.16, 129.22, 128.62, 128.53, 127.91, 127.81, 126.21, 73.59, 72.86, 65.35, 42.76, 34.64 ppm; IR (neat) 3378 (O-H), 3027 (aromatic C-H), 2857 (aliphatic C-H), 1494 (aromatic C=C), 1453 (aromatic C=C), 1362 (aromatic C=C), 1027 (C-O), 735, 696 cm^{-1}.



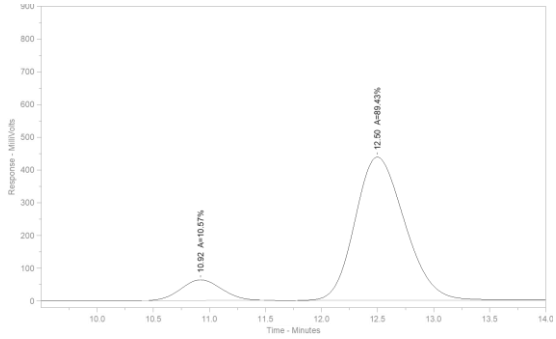
The chiral alcohol (*S*)-**103** is transformed to the chiral γ-hydroxyphosphonate (*R*)-**101** according to the procedure detailed out in Sec. 5.11.2. The chiral alcohol (*S*)-**103** (256 mg, 1.00 mmol) underwent bromination, Arbuzov rearrangement and benzyl ether cleavage to afford (*R*)-**101** (175 mg, 61%) as a colorless viscous liquid: TLC analysis (ethyl acetate/methanol 49:1) R_f = 0.5; $[\alpha]_D^{20}$ = +15° (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (5H, m, aryl), 4.16-3.98 (4H, m, b+b'), 3.77 (1H, dd, *J* = 12.0, 4.0 Hz, e(1H)), 3.59 (1H, dd, *J* = 12.0, 6.0 Hz, e(1H)), 2.79 (1H, ddd, *J* = 13.5, 7.0, 2.5 Hz, f(1H)), 2.64 (1H, dd, *J* = 13.0, 8.0 Hz, f(1H)), 2.33-2.20 (1H, m, d), 1.89-1.73 (2H, m, c), 1.33 (3H, t, *J* = 7.0 Hz, a or a'), 1.32 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.86 ppm; IR (neat) 3378 (O-H), 2981 (aromatic C-H), 2909 (aliphatic C-H), 1453 (aromatic C=C), 1391 (aromatic C=C), 1216 (P=O), 1049 (C-O), 1021 (C-O), 959 (P-O), 700 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{23}O_4P+Na^+$ = 309.1232, found 309.1230 *m/z*.

Obtaining γ-hydroxyphosphonate 101 from alkene substrate 7: Following the general procedure for CAHB (**GP4**; 6 h total reaction time), the substrate **7** (54 mg, 0.2 mmol) yields a mixture of boronic ester regioisomers and reduced products that are not separable via silica gel chromatography. The crude CAHB mixture is chromatographed (ethyl acetate/hexanes 1:1) over silica gel to get rid of the non-polar colored complex and the polar metal residues. The crude mixture obtained after this partial purification is subjected to oxidation following **GP5** to obtain the γ-hydroxyphosphonate **101** (47 mg, 71% overall from the hydroboration/oxidation sequence) as a colorless oil. Enantiomer ratio is determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC 3 micron; Mobile Phase = 80:20 Hexanes: Isopropanol; Flow rate = 1.25 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

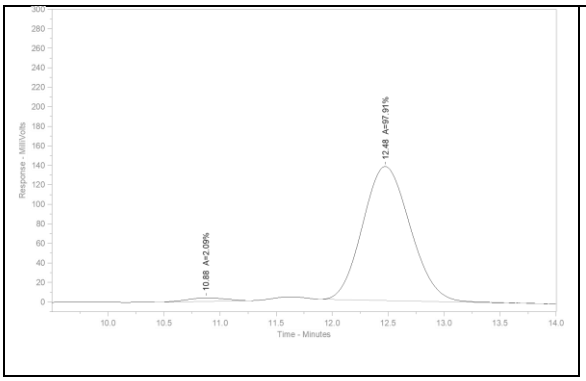
(a) R:S = 12:88, CAHB of **7** with (*R*,*R*)-**T2**, followed by oxidation to yield (*S*)-**101**:



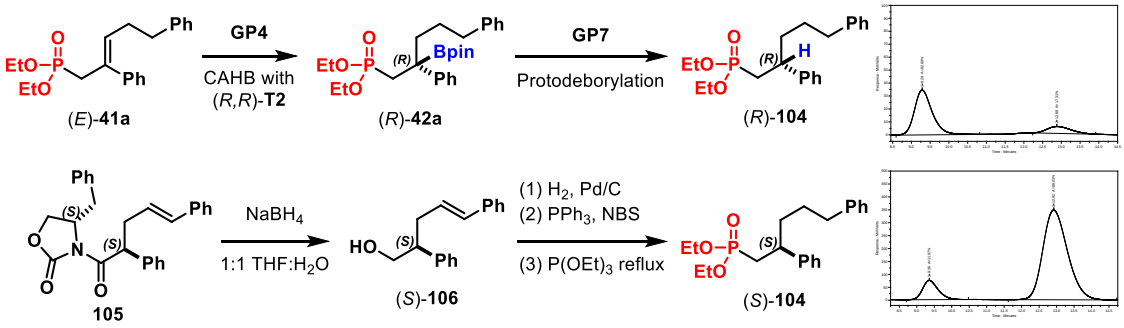
(b) R:S = 89:11, CAHB of **7** with (*S*,*S*)-**T2**, followed by oxidation to yield (*R*)-**101**:



(c) R:S = 98:2, (*R*)-**101** (enantioenriched *"R"*) obtained via chiral auxiliary sequence:



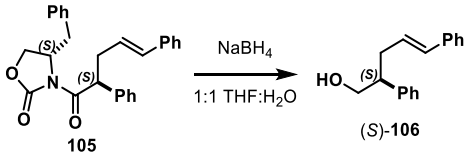
5.11.4 CAHB of β-aryl trisubstituted alkene substrate (*E*)-41a:



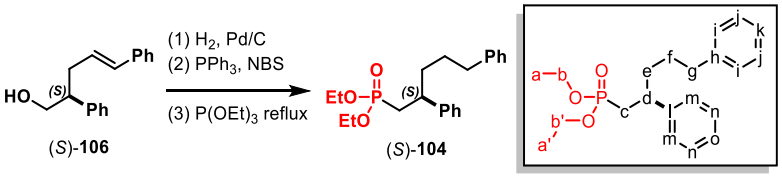
CAHB of the conjugated (β-aryl) trisubstituted substrate (*E*)-**41a** with (*R,R*)-**T2** results in the formation of chiral tertiary benzylic boronic ester product **42a**. The latter is protodeboronated (**GP7**) using conditions reported by Aggarwal to the corresponding chiral reduced product **104**. The (*S*)-enantiomer of the chiral reduced product (**104**) is obtained via asymmetric alkylation using the Evans chiral auxiliary. Chiral HPLC analysis establishes that the protodeborylated product from the chiral boronic ester is (*R*)-**104**. Since protodeborylation of chiral boronic esters proceed with retention of configuration, the configuration of the chiral boronic ester **42a** obtained from (*E*)-**41a** using (*R,R*)-**T2** is also assigned as *"R"*. The configurations of all other chiral tertiary benzylic boronic esters

derived from conjugated (β-aryl) trisubstituted substrates using (*R*,*R*)-**T2** are assigned as *"R"* by analogy.

Characterization data:



Compound **105** is prepared according to literature procedure.[45] The oxazolidinone derivative is cleaved to afford the chiral alcohol (*S*)-**106** according to the procedure outlined for the reduction of oxazolidinone derivative **99** in Sec. 5.11.2. The oxazolidinone derivative **105** (410 mg, 1.00 mmol, 1.00 eq) affords the chiral alcohol (*S*)-**106** (203 mg, 85%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 1:3) R_f = 0.5; $[\alpha]_D^{20}$ = +41° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (10H, m), 6.44 (1H, d, *J* = 16.0 Hz), 6.20-6.12 (2H, m), 3.90-3.81 (2H, m), 3.03 (1H, quin, *J* = 7.0 Hz), 2.72-2.55 (2H, m), 1.46 (br s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.99, 137.62, 131.79, 128.85, 128.60, 128.21, 128.17, 127.18, 127.02, 126.16, 66.99, 48.70, 35.99 ppm; IR (neat) 3397 (O-H), 3025 (sp^2 C-H), 2926 (sp^3 C-H), 1599 (C=C), 1493 (aromatic C=C), 1451 (aromatic C=C), 1026 (C-O), 964, 746, 692 cm^{-1}.

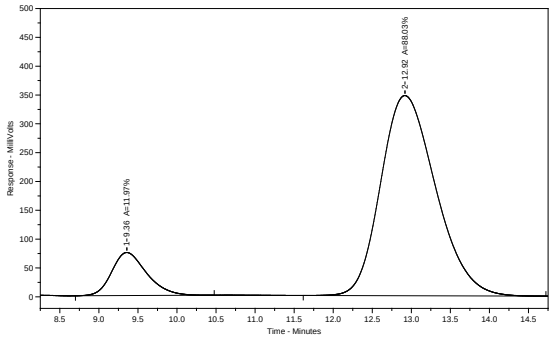


A mixture of (*S*)-**106** (191 mg, 0.80 mmol, 1.00 eq) and 10% Pd over activated carbon (10 mg) in ethanol (10 mL) is stirred under hydrogen atmosphere (balloon pressure) for 6 hours. Following this, the reaction mixture is filtered over a bed of celite to get rid of the insoluble catalyst particles. The celite bed is washed with ethanol (10 mL) and the

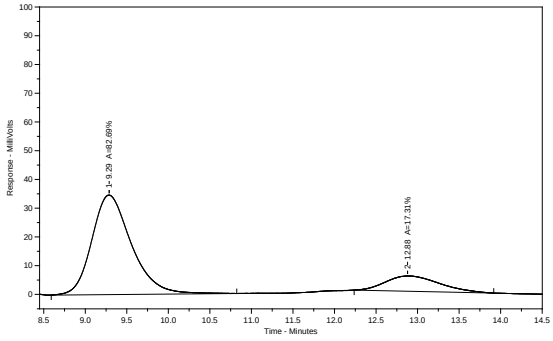
combined organics were concentrated under reduced pressure. To the resultant residue in dry dichloromethane (16 mL) at 0 ^{o}C, PPh_3 (315 mg, 1.20 mmol, 1.5 eq) and NBS (214 mg, 0.12 mmol, 1.5 eq) are sequentially added portion-wise and the resultant mixture is allowed to warm up to room temperature and stir for a total of 2 hours. Afterwards, the reaction mixture is concentrated under reduced pressure and 15 mL of 10% ethyl acetate in hexanes is added. The resultant mixture is filtered over a small pad of silica gel to get rid of the insoluble components. The silica pad is washed with 2 more portions of 15 mL of 10% ethyl acetate in hexanes and the combined organics are concentrated under reduced pressure. Triethylphosphite (0.27 mL, 1.6 mmol, 2.0 eq) is added to the resultant residue in a 10 mL round bottomed flask charged with a stirbar and the resultant mixture was refluxed vigorously under nitrogen for 1 hour. Afterwards, the volatiles are removed under reduced pressure and the residue is purified by flash chromatography over silica gel (ethyl acetate) to afford the desired chiral phosphonate product (*S*)-**104** (187 mg, 65%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +9.3^{o} (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.09 (10H, m, aryl), 4.02-3.74 (4H, m, b+b'), 3.11-3.01 (1H, m, d), 2.65-2.50 (2H, m, h), 2.13-2.07 (2H, m, c), 1.93-1.84 (1H, m, e(1H)), 1.73-1.64 (1H, m, e(1H)), 1.57-1.38 (2H, m, f), 1.21 (3H, t, *J* = 7.0 Hz, a or a'), 1.15 (3H, t, *J* = 7.0 Hz, a or a') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.57 (d, $^{3}J_{C-P}$ = 8.5 Hz, l), 142.38 (h), 128.55 (aryl), 128.48 (aryl), 128.36 (aryl), 127.66 (aryl), 126.61 (aryl), 125.79 (aryl), 61.43 (d, $^{2}J_{C-P}$ = 7.0 Hz, b or b'), 61.26 (d, $^{2}J_{C-P}$ = 6.5 Hz, b or b'), 40.29 (d, $^{2}J_{C-P}$ = 3.5 Hz, d), 37.45 (d, $^{3}J_{C-P}$ = 12.0 Hz, e), 35.79 (g), 33.39 (d, $^{1}J_{C-P}$ = 139 Hz, c), 29.15 (f), 16.43 (d, $^{3}J_{C-P}$ = 7.0 Hz, a or a'), 16.41 (d, $^{3}J_{C-P}$ = 7.0 Hz, a or a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.18 ppm; IR (neat) 3026 (sp^2 C-H), 2933 (sp^3 C-H), 1495 (aromatic C=C), 1453

(aromatic C=C), 1241 (P=O), 1053 (C-O), 1024 (C-O), 955 (P-O), 697 cm^{-1}. HRMS (EI) calculated for $C_{21}H_{29}O_3P$ = 360.1854, found 360.1843 *m/z*. Enantiomer ratio is determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 20:80 Hexanes:Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

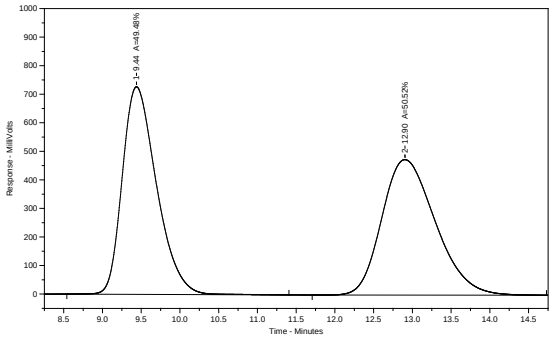
(a) R:S = 12:88, **104** synthesized via chiral auxiliary synthesis:



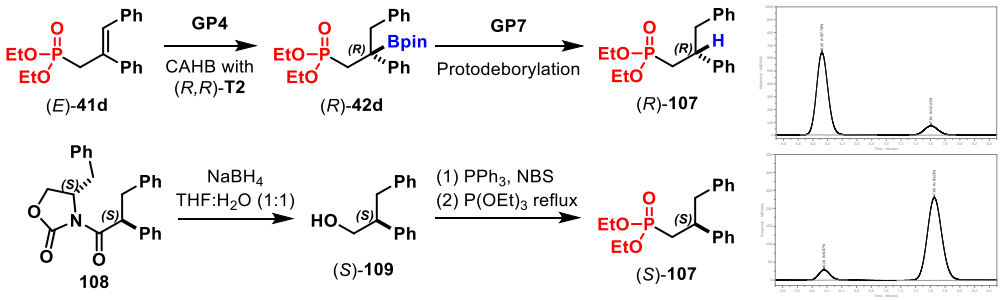
(b) R:S = 83:17, CAHB of (*E*)-**41a** with (*R*,*R*)-**T2** to form **42a** and then protodeboronation to form **104**:



(c) Racemic mixture of **104** obtained by hydrogenation of (*E*)-**41a** with H_2 over Pd/C:

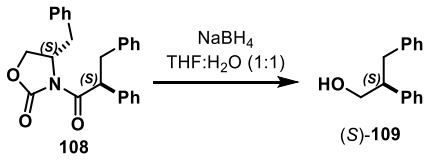


5.11.5 CAHB of β,γ-diaryl trisubstituted alkene substrate (*E*)-41d:



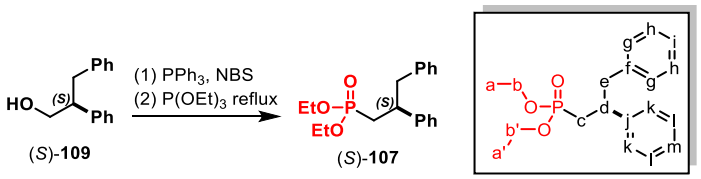
CAHB of the β,γ-diphenyl trisubstituted substrate (*E*)-**41d** with (*R*,*R*)-**T2** results in β-borylation with the formation of chiral tertiary benzylic boronic ester product **42d**. The latter is protodeboronated using **GP7** to afford the corresponding chiral reduced product with the retention of configuration at the chiral carbon.[8] Enantioenriched (*S*)-**107** is obtained via asymmetric alkylation using the Evans chiral auxiliary to give the known chiral alcohol (*S*)-**109**.[46] Chiral HPLC analysis shows that the protodeborylated product obtained from the chiral tertiary boronic ester **42d** is (*R*)-**107**.

Characterization Data:



Compound **108** is prepared as previously reported.[47] The oxazolidinone derivative **108** is cleaved to afford the chiral alcohol (*S*)-**109** according to the procedure outlined for the reduction of oxazolidinone derivative **99** in Sec. 5.11.2. The oxazolidinone derivative **108** (385 mg, 1.00 mmol, 1.00 eq) affords the chiral alcohol (*S*)-**109** (174 mg, 82%) as a colorless oil: TLC analysis (ethyl acetate/hexanes 1:3) R_f = 0.5; $[\alpha]_D^{20}$ = +49° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.11 (10H, m), 3.86-3.77 (2H, m), 3.16-2.92 (3H, m), 1.34 (1H, t, *J* = 6.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.11, 140.12,

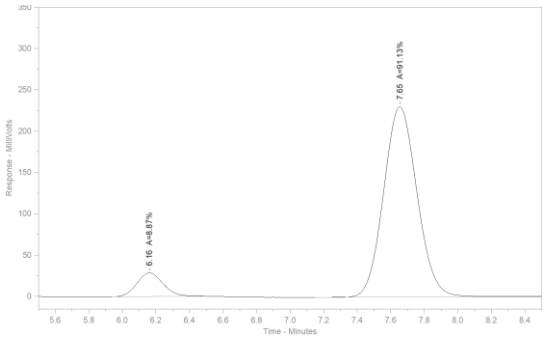
129.26, 128.84, 128.45, 128.30, 127.06, 126.23, 66.57, 50.39, 38.91 ppm; IR (neat) 3320 (O-H), 3025 (sp^2 C-H), 2920 (sp^3 C-H), 1601, 1494 (aromatic C=C), 1451 (aromatic C=C), 1060 (C-O), 1028 (C-O), 757, 695 cm^{-1}.



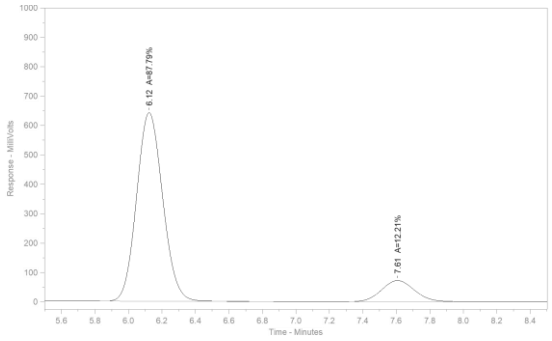
To a solution of the chiral alcohol (*S*)-**109** (106 mg, 0.5 mmol, 1.0 eq) in dry dichloromethane (10 mL) is added PPh_3 (197 mg, 0.75 mmol, 1.50 eq) and the resultant solution is cooled down to 0°C. To the resultant solution NBS (134 mg, 0.75 mmol, 1.50 eq) is added portion wise and the resultant mixture is allowed to warm up to room temperature and stirred for a total of 2 hours. Afterwards, the reaction mixture is concentrated under reduced pressure and 10 mL of 15% ethyl acetate in hexanes is added. The resultant mixture is filtered over a small pad of silica gel to get rid of the insoluble components. The silica pad is washed with 2 more portions of 10 mL of 10% ethyl acetate in hexanes and the combined organics are concentrated under reduced pressure. To the resultant residue triethylphosphite (0.17 mL, 1.0 mmol, 2.0 eq) is added and the resultant mixture refluxed vigorously under nitrogen atmosphere for 2 hours. Afterwards, the volatiles were removed under reduced pressure and the residue is purified by flash chromatography over silica gel (ethyl acetate) to afford the desired chiral phosphonate product (*S*)-**107** (116 mg, 70%) as a colorless oil: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +34° (*c* = 1.0, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 7.28-7.26 (2H, m, aryl), 7.23-7.15 (6H, m, aryl), 7.03 (2H, d, *J* = 7.0 Hz, aryl), 3.97-3.91 (1H, m, b or b'), 3.90-3.84 (2H, m, b or b'), 3.74-3.68 (1H, m, b or b'), 3.35-3.29 (1H, m, d), 3.05 (1H, dd, *J* = 13.5, 7.5 Hz, e (1H)), 2.94 (1H, ddd, *J* = 13.5, 7.5, 1.5 Hz, e (1H)), 2.22-2.11 (2H, m, c), 1.18

(3H, t, J = 7.0 Hz, a or a'), 1.13 (3H, t, J = 7.0 Hz, a or a') ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 143.99 (d, $^3J_{C\text{-}P}$ = 7.0 Hz, j), 139.56 (f), 129.51 (aryl), 128.46 (aryl), 128.36 (aryl), 127.91 (aryl), 126.75 (aryl), 126.35 (aryl), 61.56 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 61.34 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b or b'), 44.70 (d, $^3J_{C\text{-}P}$ = 14.0 Hz, e), 42.46 (d, $^2J_{C\text{-}P}$ = 3.5 Hz, d), 31.75 (d, $^1J_{C\text{-}P}$ = 139 Hz, c), 16.44 (d, $^3J_{C\text{-}P}$ = 6.5 Hz, a+a') ppm; ^{31}P NMR (283 MHz, $CDCl_3$) δ 30.09 ppm; IR (neat) 3018 (sp^2 C-H), 2943 (sp^3 C-H), 1496 (aromatic C=C), 1451 (aromatic C=C), 1239 (P=O), 1051 (C-O), 1025 (C-O), 955 (P-O), 698 cm^{-1}. HRMS (EI) calculated for $C_{19}H_{25}O_3P$ = 332.1541, found = 332.1538 *m/z*. Enantiomer ratio is determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 20:80 Hexanes: Isopropanol; Flow rate = 1 mL/min. HPLC UV detector λ = 210 nm, rt. HPLC traces:

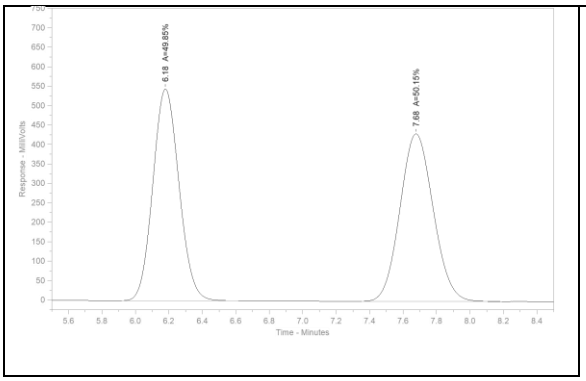
(a) R:S = 9:91, **107** synthesized via chiral auxiliary synthesis:



(b) R:S = 88:12, CAHB of (*E*)-**41d** with (*R,R*)-**T2** to form **42d** which protodeboronates to form **107**.

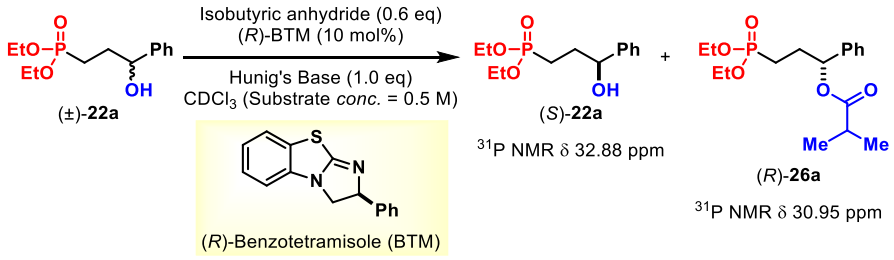


(c) Racemic mixture of **107** obtained by hydrogenation of (*E*)-**41d** with H_2 over Pd/C:



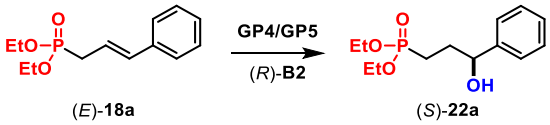
5.11.6. Kinetic Acylation of Chiral Secondary Benzylic Alcohols using Benzotetramisole (BTM)

Benzotetramisole is prepared according to Birman's previously reported procedure.[48] For carrying out enantioselectivity tests, the general guided reaction of kinetic acylation using Benzotetramisole (BTM) for a racemic mixture of chiral secondary benzyl alcohol **22a** is shown below. (*R*)-BTM catalyzes the esterification reaction of (*R*)-enantiomer of the chiral secondary benzylic alcohol with isobutyric anhydride faster than the (*S*)-enantiomer and vice-versa.



General Procedure for Absolute Configuration Assignment via Enantioselectivity Test (GP18): The absolute configuration assignments based on enantioselectivity tests were carried out according to the procedure reported by Birman and coworkers as follows.

The stock solution of the kinetic acylation catalyst is prepared by dissolving 0.05 mmol of BTM and 0.75 mmol of Hunig's base in 1 mL $CDCl_3$ (dried over activated molecular sieves). The racemic mixture of the chiral secondary benzylic alcohol (0.25 mmol) is taken in an oven dried glass vial and to this, 0.5 mL of the stock solution of the catalyst is added. To this, propionic anhydride (0.15 mmol, 0.6 eq) is added (stopwatch started at this point), the contents were mixed and transferred to an NMR tube. The reaction is monitored by ^{31}P NMR by comparing the integration values of the peak corresponding to the starting alcohol and the new peak appearing upfield (corresponding to the anhydride). When the relative ratios of the two species are about 1:1, the reaction mixture is quenched by pouring the contents into a vial containing MeOH. Standard workup and HPLC analysis were carried out afterwards.



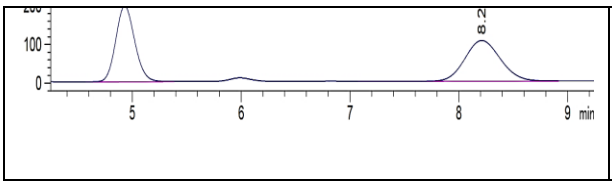
(*E*)-**18a** (*S*)-**22a**

Absolute configuration assignment of alcohol 22a obtained from (*E*)**-18a following GP4 using** (*R*)**-B2 followed by oxidation (GP5):** *Rac*-**22a** is subjected to kinetic acylation according to **GP18** using (*R*)-BTM. Matching the HPLC traces of unreacted **22a** after kinetic acylation with that of **22a** obtained from (*E*/*Z*)-**5a** after CAHB/Oxidation sequence (**GP4** using (*R*)-**B2**) suggests that (*S*)-**22a** is forming in the CAHB/Oxidation sequence of **18a** with (*R*)-**B2**.

Alcohol **22a** is also a previously reported compound in the literature. Negative value of optical rotation obtained for **22a** (obtained via CAHB/Oxidation sequence of (*E*/*Z*)-**18a** (**GP4**) using (*R*)-**B2**) is also in lines with what would be expected for the (*S*)-enantiomer.[12]

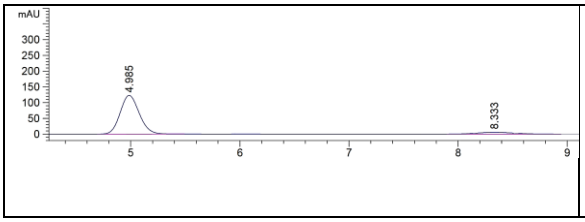
HPLC traces are shown below:

(a) Racemate



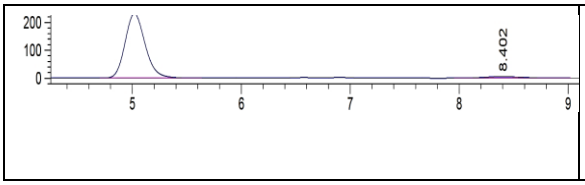
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.930	BB	0.1873	2383.36279	50.0002
2	8.210	VB	0.3529	2383.34546	49.9998

(b) After kinetic resolution of *rac*-**22a** using (*R*)-BTM. Major peak corresponds to (*S*)-**22a**.

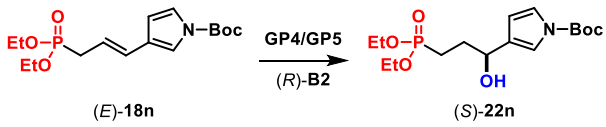


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.985	BB	0.1883	1486.30774	92.225
2	8.333	BB	0.3563	125.29859	7.774

(c) **22a** formed via CAHB of (*E*/Z)-**18a** using (*R*)-**B2** followed by oxidation (R:S = 4:96). Major peak corresponds to (*S*)-**22a**.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.018	BB	0.1972	2961.21484	95.766
2	8.402	BB	0.3608	130.91283	4.233

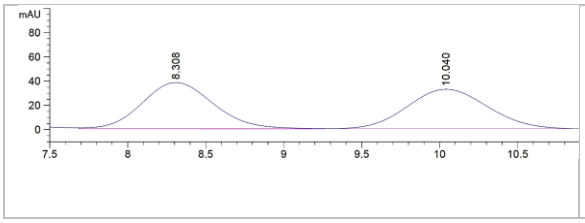


(*E*)-**18n** (*S*)-**22n**

Absolute configuration assignment of alcohol 22n obtained from (*E*)-18n following GP4 using (*R*)-B2 followed by oxidation (GP5): *Rac*-**22n** is subjected to kinetic acylation according to **GP18** using (*R*)-BTM. Matching the HPLC traces of unreacted **22n** after

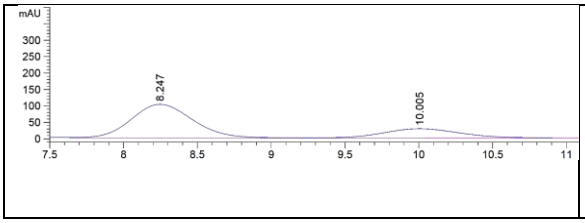
kinetic acylation with that of **22n** obtained from (*E*)-**18n** after CAHB/Oxidation sequence (**GP4** using (*R*)-**B2**) suggests that (*S*)-**22n** is forming in the CAHB/Oxidation sequence of (*E*)-**18n** with (*R*)-**B2**. HPLC traces are shown below:

(a) Racemate



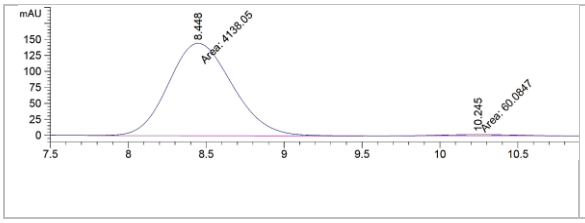
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.308	VB	0.4999	1220.43323	50.782
2	10.040	BB	0.5680	1182.84241	49.217

(b) After kinetic resolution of *rac*-**22n** using (*R*)-BTM. Major peak corresponds to (*S*)-**22n**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.247	VB	0.4523	2985.92114	74.899
2	10.005	BB	0.5597	1000.65094	25.100

(c) **22n** formed via CAHB of (*E*)-**18n** using (*R*)-**B2** followed by oxidation (R:S = 1:99). Major peak corresponds to (*S*)-**22n**.

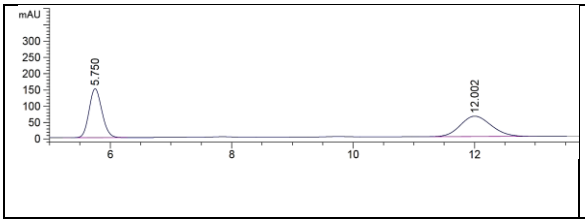


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.448	MM	0.4770	4138.04736	98.568
2	10.245	MM	0.5194	60.08473	1.431

(*E*)-**18q** (*S*)-**22q**

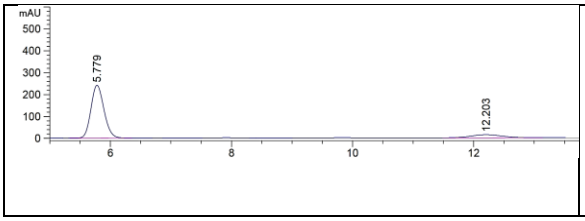
Absolute configuration assignment of alcohol 22q obtained from (*E*)**-18q following GP4 using** (*R*)**-B2 followed by oxidation (GP5):** *Rac*-**22q** is subjected to kinetic acylation according to **GP18** using (*R*)-BTM. Matching the HPLC traces of unreacted **22q** after kinetic acylation with that of **22q** obtained from (*E*)-**18q** after CAHB/Oxidation sequence (**GP4** using (*R*)-**B2**) suggests that (*S*)-**22q** is forming in the CAHB/Oxidation sequence of **18q** with (*R*)-**B2**. HPLC traces are shown below:

(a) Racemate



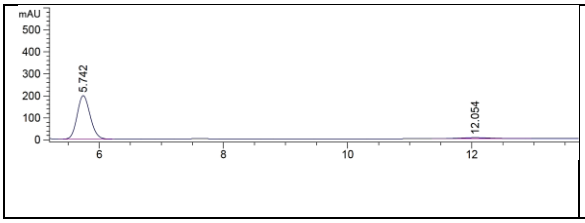
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.750	VB	0.2283	2203.71069	49.891
2	12.002	BB	0.5534	2213.28174	50.108

(b) After kinetic resolution of *rac*-**22q** using (*R*)-BTM. Major peak corresponds to (*S*)-**22q**.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.779	BB	0.2320	3595.21875	87.906
2	12.203	BB	0.5500	494.58777	12.093

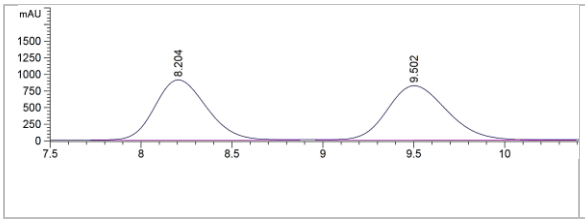
(c) **22q** formed via CAHB of (*E*)-**18q** using (*R*)-**B2** followed by oxidation (R:S = 5:95). Major peak corresponds to (*S*)-**22q**.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.742	VB	0.2264	2871.94727	95.098
2	12.054	BB	0.5312	148.02408	4.901

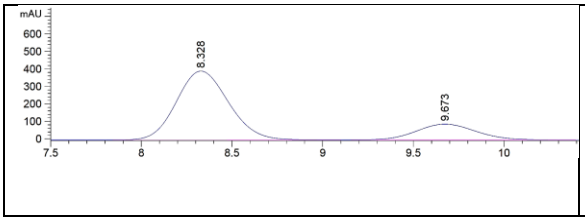
Absolute configuration assignment of alcohol 22x obtained from (*E*)**-18x following GP4 using** (*R*)**-B2 followed by oxidation (GP5):** *Rac*-**22x** is subjected to kinetic acylation according to **GP18** using (*R*)-BTM. Matching the HPLC traces of unreacted **22x** after kinetic acylation with that of **22x** obtained from (*E*)-**18x** after CAHB/Oxidation sequence (**GP4** using (*R*)-**B2**) suggests that (*S*)-**22x** is forming in the CAHB/Oxidation sequence of (*E*)-**18x** with (*R*)-**B2**. HPLC traces are shown below:

(a) Racemate



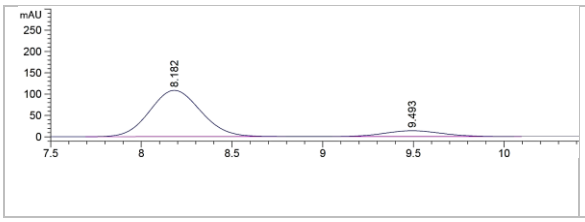
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.204	VB	0.3104	1.82104e4	48.910
2	9.502	BB	0.3593	1.90216e4	51.089

(b) After kinetic resolution of *rac*-**22x** using (*R*)-BTM. Major peak corresponds to (*S*)-**22x**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.328	VB	0.3121	7869.70459	79.291
2	9.673	BB	0.3552	2055.31274	20.708

(c) **22x** formed via CAHB of (*E*)-**18x** using (*R*)-**B2** followed by oxidation (R:S = 12:88). Major peak corresponds to (*S*)-**22x**.

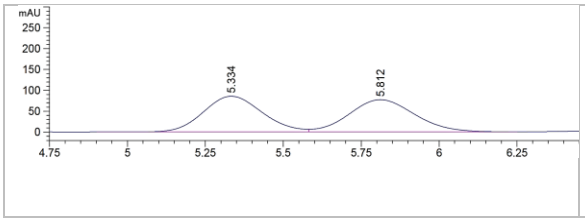


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	8.182	BB	0.3053	2122.38354	87.749
2	9.493	BB	0.3435	296.31558	12.251

(*E*/*Z*)-**23** (*S*)-**25**

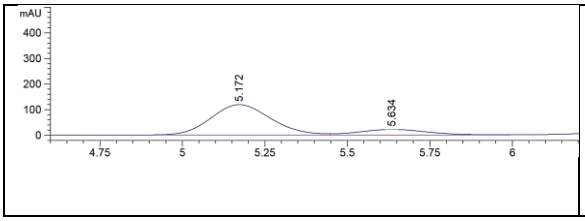
Absolute configuration assignment of alcohol 25 obtained from (*E*/Z)-**23 following GP4 using** (*R*)-**B2 followed by oxidation (GP5):** *Rac*-**25** is subjected to kinetic acylation according to **GP18** using (*R*)-BTM. Matching the HPLC traces of unreacted **25** after kinetic acylation with that of **25** obtained from (*E*/*Z*)-**23** after CAHB/Oxidation sequence (**GP4** using (*R*)-**B2**) confirmed that (*S*)-**25** is forming in the CAHB/Oxidation sequence of (*E*/*Z*)-**23** with (*R*)-**B2**. HPLC traces are shown below:

(a) Racemate



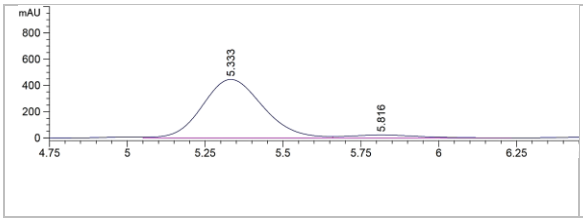
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.334	BV	0.2044	1125.28809	49.766
2	5.812	VV	0.2276	1135.86536	50.233

(b) After kinetic resolution of *rac*-**25** using (*R*)-BTM. Major peak corresponds to (*S*)-**25**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.172	BV	0.1969	1500.03491	83.159
2	5.634	VV	0.2183	303.76675	16.840

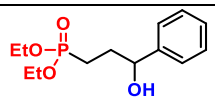
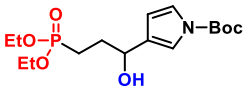
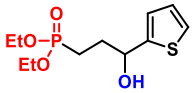
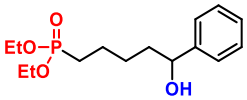
(c) **25** formed via CAHB of (*E*/*Z*)-**23** using (*R*)-**B2** followed by oxidation (R:S = 5:95). Major peak corresponds to (*S*)-**25**.

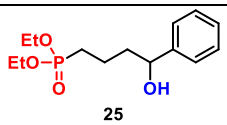


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.333	VV	0.2092	6003.92041	94.589
2	5.816	VV	0.2342	343.43286	5.410

For the above 5 cases, absolute configuration is assigned based on enantioselectivity tests. The conversion (*c*) is estimated via NMR analysis. The selectivity factor (*s*)[49] is calculated using the following formula:

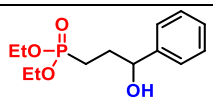
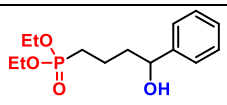
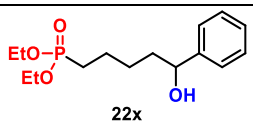
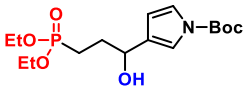
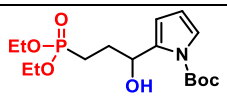
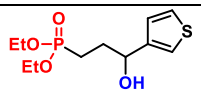
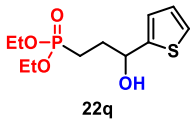
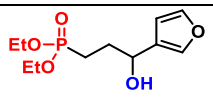
$$s = \ln[(1-c)(1-ee)]/\ln[(1-c)(1+ee)]$$

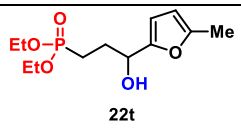
Entry	Substrate	ee of recovered alcohol	Conversion (via NMR)	Selectivity factor (*s*)
1	 22a	84.45%	49%	41.45
2	 22n	49.80%	46%	6.15
3	 22q	75.81%	47%	29.08
4	 22x	58.58%	40%	28.00

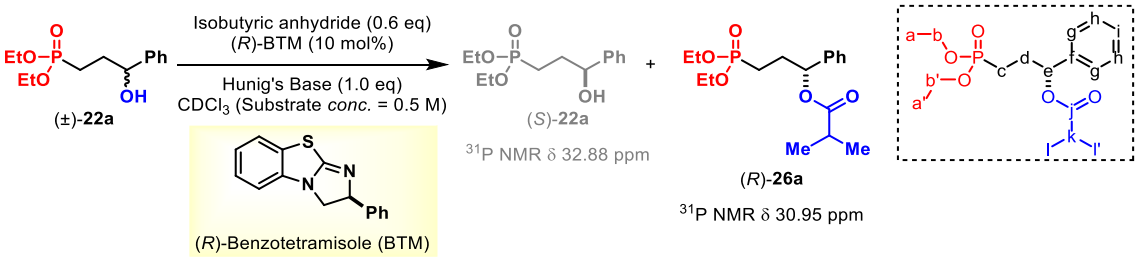
5	 25	66.32%	40%	45.38

General Procedure for Absolute Configuration Assignment based on the Relative Speed of Ester Formation from Chiral Secondary Benzylic Alcohol (Obtained via CAHB/Oxidation sequence) using (*R*)- and (*S*)- BTM (GP19): Two separate stock solutions of (*R*)- and (*S*)-BTM were prepared as follows. 25 μmol of BTM and 0.4 mmol of Hunig's base are taken up in 1 mL $CDCl_3$ (dried over activated molecular sieves). The chiral secondary benzylic alcohol (0.25 mmol; Obtained using **GP4** with (*R*)-**B2** followed by oxidation (**GP5**)) is weighed in two separate labelled oven dried glass vials and in one vial 0.5 mL of the stock solution of (*R*)-BTM is added. In the second vial, 0.5 mL of the stock solution of (*S*)-BTM is added. To each vial propionic anhydride (0.15 mmol, 0.6 eq) is added and (timer started at this point), the contents were mixed and transferred to an NMR tube. The reactions are monitored by ^{31}P NMR spectroscopy for the appearance of an upfield peak corresponding to the ester. Since (*R*)-BTM catalyzes reaction of (*R*)-enantiomer of a chiral secondary benzylic alcohol with propionic anhydride faster than the (*S*)-enantiomer and vice-versa, the absolute configuration is assigned based on which configuration of BTM leads to the faster formation of the anhydride.

Entry	Alcohol obtained via **GP4** (Using (*R*)-**B2**) followed by oxidation (**GP5**)	% Ester formation using (*R*)-BTM	% Ester formation using (*S*)-BTM	Absolute Configuration

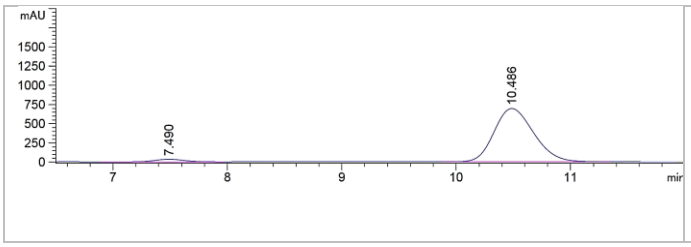
1	 22a	5% in 30 minutes	50% in 30 minutes	*"S"*
2	 25	3% in 30 minutes	45% in 30 minutes	*"S"*
3	 22x	5% in 30 minutes	47% in 30 minutes	*"S"*
4	 22n	2% in 12 hours	27% in 12 hours	*"S"*
5	 22o	21% in 12 hours	3% in 12 hours	*"R"*
6	 22p	4% in 1 hour	30% in 1 hour	*"S"*
7	 22q	2% in 1 hour	31% in 1 hour	*"S"*
8	 22s	6% in 12 hours	41% in 12 hours	*"S"*

9	 22t	3% in 12 hours	14% in 12 hours	*"S"*



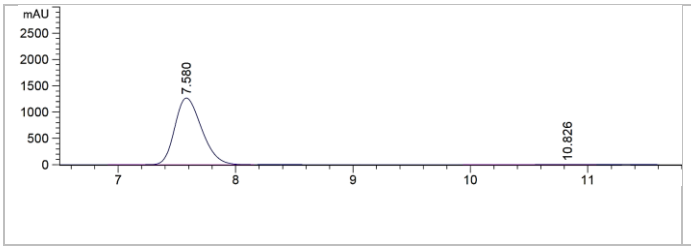
Characterization data of (*R*)-**26a**: TLC analysis (ethyl acetate) R_f = 0.5; $[\alpha]_D^{20}$ = +47° (*c* = 1.0, $CHCl_3$; Optical rotation of *"R"* enantiomer); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (5H, m, aryl), 5.76 (1H, dd, *J* = 7.0, 6.0 Hz, e), 4.13-4.00 (4H, m, b+b'), 2.58 (1H, sept, *J* = 7.0 Hz, k), 2.23-2.02 (2H, m, d), 1.82-1.62 (2H, m, c), 1.30 (6H, t, *J* = 7.0 Hz, a+a'), 1.18 (3H, d, *J* = 7.0 Hz, l or l'), 1.15 (3H, d, *J* = 7.0 Hz, l or l') ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.08 (l), 139.99 (f), 128.69 (h), 128.19 (i), 126.42 (g), 75.26 (d, $^3J_{C\text{-}P}$ = 19 Hz, e), 61.75 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, b+b'), 34.27 (k), 29.61 (d, $^2J_{C\text{-}P}$ = 4.25 Hz, d), 22.11 (d, $^1J_{C\text{-}P}$ = 143 Hz, c), 19.05 (l or l'), 19.00 (l or l'), 16.54 (d, $^3J_{C\text{-}P}$ = 5.9 Hz, a+a') ppm; ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.95 ppm; IR (neat) 2976 (C-H), 1732 (C=O), 1470 (aromatic C=C), 1455 (aromatic C=C), 1387 (aromatic C=C), 1244 (P=O), 1053 (C-O), 1022 (C-O), 955 (P-O), 699 cm^{-1}. Enantiomer ratio = 99:1, determined by chiral HPLC analysis: Stationary phase = CHIRALPAK IC; Mobile Phase = 50:50 Isopropanol:Hexanes; Flow rate = 1 mL/min; HPLC UV Detector λ = 210 nm, 25 °C. HPLC traces:

(a) R:S = 96:4, Reaction of *rac*-**22a** with 0.6 eq. isobutyric anhydride with (*R*)-BTM. Ester **26a** formed is enriched in *"R"* enantiomer.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	7.490	VB	0.2798	628.97388	3.6464
2	10.486	BB	0.3750	1.66201e4	96.3536

(b) R:S = 1:99, Reaction of *rac*-**22a** with 0.6 eq. isobutyric anhydride with (*S*)-BTM. Ester **26a** formed is enriched in *"S"* enantiomer.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	7.580	VV	0.2481	2.02153e4	99.218
2	10.826	VV	0.4515	159.21370	0.781

5.12. Reference

(1) Ohmura, T.; Masuda, K.; Takase, I.; Suginome, M. "Palladium-Catalyzed Silylene-1,3-Diene [4 + 1] Cycloaddition with Use of (Aminosilyl)boronic Esters as Synthetic Equivalents of Silylene" *J. Am. Chem. Soc.* **2009**, *131*, 16624.

(2) Kim, D. D.; Lee, S. J.; Beak, P. "Asymmetric Lithiation−Substitution Sequences of Substituted Allylamines" *J. Org. Chem.* **2005**, *70*, 5376.

(3) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. "Total Synthesis of Ionomycin Using Ring-Opening Strategies" *Org. Lett.* **2002**, *4*, 1879.

(4) Garzan, A.; Jaganathan, A.; Marzijarani, N. S.; Yousefi, R.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. "Solvent-Dependent Enantiodivergence in the Chlorocyclization of Unsaturated Carbamates" *Chem. Eur. J.* **2013**, *19*, 9015.

(5) Orimoto, K.; Oyama, H.; Namera, Y.; Niwa, T.; Nakada, M. "Catalytic Asymmetric [4 + 2] Cycloadditions and Hosomi–Sakurai Reactions of α-Alkylidene β-Keto Imides" *Org. Lett.* **2013**, *15*, 768.

(6) Wegmann, M.; Bach, T. "Stereoselective Synthesis of a Highly Oxygenated δ-Lactone Related to the Core Structure of (–)-Enterocin" *Synthesis* **2017**, *49*, 209.

(7) Zhang, L.; Liu, W.; Zhao, X. "Carbon–Phosphorus Bond Formation by Enantioselective Palladium-Catalyzed Allylation of Diphenylphosphine Oxide" *Eur. J. Org. Chem.*, 2014, **31**, 6846.

(8) Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kuehnle, F. N. M. "On the Ti-TADDOLate-Catalyzed Diels-Alder Addition of 3-Butenoyl-1,3-oxazolidin-2-one to Cyclopentadiene. General Features of Ti-BINOLate- and Ti-TADDOLate-Mediated Reactions" *J. Org. Chem.*, **1995**, *60*, 1788.

(9) Smith, S. M.; Thacker, N. C.; Takacs, J. M. "Efficient Amide-Directed Catalytic Asymmetric Hydroboration" *J. Am. Chem. Soc.*, **2008**, *130*, 3734.

(10) See, J. Y.; Yang, H.; Zhao, Y.; Wong, M. W.; Ke, Z.; Yeung, Y. Y. "Desymmetrizing Enantio- and Diastereoselective Selenoetherification through Supramolecular Catalysis" *ACS Catal.*, **2018**, *8*, 850.

(11) Hoang, G. L.; Yang, Z. D.; Smith, S. M.; Pal, R.; Miska, J. L.; Pérez, D. E.; Pelter, L. S. W.; Zeng, X. C.; Takacs, J. M. "Enantioselective Desymmetrization via Carbonyl-Directed Catalytic Asymmetric Hydroboration and Suzuki–Miyaura Cross-Coupling" *Org. Lett.*, **2015**, *17*, 940.

(12) (a) Xiong, Y.; Zhang, G. "Enantioselective Synthesis of Quaternary Stereocenters via Chromium Catalysis" *Org. Lett.*, **2016**, *18*, 5094. (b) Esumi, T.; Yamamoto, C.; Fukuyama,

Y. "A Short Synthesis of (+)-Bakuchiol" *Synlett.*, **2013**, *24*, 1845. (c) Gao, F.; McGrath, K. P.; Lee, Y. Hoveyda, A. H. "Synthesis of Quaternary Carbon Stereogenic Centers through Enantioselective Cu-Catalyzed Allylic Substitutions with Vinylaluminum Reagents" *J. Am. Chem. Soc.*, **2010**, *132*, 14315.

(13) Zhang, Y. H.; Xu, C. F.; Li, J. F.; Yuan, C. Y. "Candida rugosa Lipase-catalyzed Kinetic Resolution of Hydroxy-alkanephosphonates", *Chin. J. Chem.*, **2003**, *21*, 883.

(14) Kamal, A.; Sandbhor, M.; Shaik, A. A. "Application of a one-pot lipase resolution strategy for the synthesis of chiral γ- and δ-lactones" *Tetrahedron Asymmetry*, **2003**, *14*, 1575.

(15) Zurawinski, R.; Nakamura, K.; Drabowicz, J.; Kielbasinski, P.; Mikołajczyk, M. "Biocatalytic syntheses of chiral non-racemic 2-hydroxyalkanephosphonates" *Tetrahedron Asymmetry*, **2001**, *12*, 3139.

(16) Bagutski, V.; Ros, A.; Aggarwal, V. K. "Improved method for the conversion of pinacolboronic esters into trifluoroborate salts: facile synthesis of chiral secondary and tertiary trifluoroborates" *Tetrahedron* **2009**, *65*, 9956.

(17) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. "Protodeboronation of Tertiary Boronic Esters: Asymmetric Synthesis of Tertiary Alkyl Stereogenic Centers" *J. Am. Chem. Soc.*, **2010**, *132*, 17096.

(18) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. "Enantiospecific sp^2–sp^3 coupling of secondary and tertiary boronic esters" *Nat. Chem.* **2014**, *6*, 584.

(19) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. "Enantioselective Construction of Quaternary Stereogenic Centers from

Tertiary Boronic Esters: Methodology and Applications" *Angew. Chem., Int. Ed.,* **2011**, *50*, 3760.

(20) Hong, Y-S.; Lin, S. W.; Lu, L.; Chen, Y-J. "The mechanistic study and synthetic applications of the base treatment in the ozonolytic reactions" *Tetrahedron.*, **1995**, *51*, 5019.

(21) Zhang, L.; Zuo, Z.; Wan, Z.; Zheng, H. "Cobalt-Catalyzed Enantioselective Hydroboration of 1,1-Disubstituted Aryl Alkenes" *J. Am. Chem. Soc.*, **2014**, *136*, 15501.

(22) Chatterjee, B.; Gunanathan, C. "Ruthenium catalyzed selective hydrosilylation of aldehydes" *Chem. Commun.*, **2014**, *50*, 888.

(23) Patel, H. H.; Sigman, M. S. "Enantioselective Palladium-Catalyzed Alkenylation of Trisubstituted Alkenols To Form Allylic Quaternary Centers" *J. Am. Chem. Soc.*, **2016**, *138*, 14226.

(24) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. "Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures" *J. Org. Chem.*, **1996**, *61*, 3849.

(25) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. "Cross Coupling Reactions of Chiral Secondary Organoboronic Esters With Retention of Configuration" *J. Am. Chem. Soc.*, **2009**, *131*, 5024.

(26) Hu, N.; Zhao, G.; Zhang, Y.; Liu, X.; Li, G.; Tang, W. "Synthesis of Chiral α-Amino Tertiary Boronic Esters by Enantioselective Hydroboration of α-Arylenamides" *J. Am. Chem. Soc.*, **2015**, *137*, 6746.

(27) Ros, A.; Aggarwal, V. K. "Complete stereoretention in the rhodium-catalyzed 1,2-addition of chiral secondary and tertiary alkyl potassium trifluoroborate salts to aldehydes" *Angew. Chem., Int. Ed.*, **2009**, *48*, 6289.

(28) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. "Ate Complexes of Secondary Boronic Esters as Chiral Organometallic-Type Nucleophiles for Asymmetric Synthesis" *J. Am. Chem. Soc.*, **2011**, *133*, 16794.

(29) Pogatchnik, D. M.; Weimer, D. F. "Enantioselective synthesis of α-hydroxy phosphonates via oxidation with (camphorsulfonyl)oxaziridines" *Tett. Lett.* **1997**, *38*, 3495.

(30) Rowe, B. J.; Spilling, C. D. "Stereospecific Pd(0)-Catalyzed Arylation of an Allylic Hydroxy Phosphonate Derivative: Formal Synthesis of (S)-(+)-ar-Turmerone" *J. Org. Chem.*, **2003**, *68*, 9502.

(31) Jang, K. P.; Hutson, G. E.; Johnston, R. C. McCusker, E. O.; Cheong, P. H. Y.; Scheidt, K. A. "Asymmetric Homoenolate Additions to Acyl Phosphonates through Rational Design of a Tailored N-Heterocyclic Carbene Catalyst" *J. Am. Chem. Soc.* **2014**, *136*, 76.

(32) Tan, J.; Cheon, C-H.; Yamamoto, H. "Construction of Vicinal Tertiary and All Carbon Quaternary Centers by Catalytic Asymmetric Claisen Rearrangement of Enolphosphonates" *Angew. Chem. Int. Ed.* **2012**, *51*, 8264.

(33) Gao, M.; Wang, D-X.; Zheng, Q-Y.; Huang, Z-T.; Wang, M-X. "Remarkable Electronic and Steric Effects in the Nitrile Biotransformations for the Preparation of Enantiopure Functionalized Carboxylic Acids and Amides: Implication for an Unsaturated Carbon−Carbon Bond Binding Domain of the Amidase" *J. Org. Chem.* **2007**, *72*, 6060.

(34) Liu, Y.; Liu, X.; Hu, H.; Guo, J.; Xia, Y.; Lin, L.; Feng, X. "Synergistic Kinetic Resolution and Asymmetric Propargyl Claisen Rearrangement for the Synthesis of Chiral Allenes" *Angew. Chem., Int. Ed.* **2016**, *55*, 4054.

(35) Zhu, Q.; Lu, Y. "Chiral primary amine mediated conjugate addition of branched aldehydes to vinyl sulfone: asymmetric generation of quaternary carbon centers" *Chem. Commun.* **2010**, *46*, 2235.

(36) Evans, P. A.; Oliver, S.; Chae, J. "Rhodium-Catalyzed Allylic Substitution with an Acyl Anion Equivalent: Stereospecific Construction of Acyclic Quaternary Carbon Stereogenic Centers" *J. Am. Chem. Soc.* **2012**, *134*, 19314.

(37) Maeda, H.; Takahashi, K.; Ohmori, H. "Reactions of acyl tributylphosphonium chlorides and dialkyl acylphosphonates with Grignard and organolithium reagents" *Tetrahedron* **1998**, *54*, 12233.

(38) Parikh, J. R.; Doering, W. v. E. "Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide" *J. Am. Chem. Soc.*, **1967**, *89*, 5505.

(39) Yamagishi, T.; Muronoi, S.; Hikishima, S.; Shimeno, H.; Soeda, S.; Yokomatsu, T. "Diastereoselective Synthesis of γ-Amino-δ-hydroxy-α,α-difluorophosphonates: A Vehicle for Structure−activity Relationship Studies on SMA-7, a Potent Sphingomyelinase Inhibitor" *J. Org. Chem.*, **2009**, *74*, 6350; and references cited therein.

(40) Corey, E. J.; Kwiatkowski, G. T. "The Synthesis of Olefins from O,O'-Dialkyl β-Lithioalkylphosphonothioate Esters" *J. Am. Chem. Soc.*, **1966**, *88*, 5654.

(41) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. "Rhodium-Catalyzed Asymmetric 1,4-Addition to 1-Alkenylphosphonates" *J. Am. Chem. Soc.*, **1999**, *121*, 11591.

(42) Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B. T.; Katz, C. E.; Reddy, D. S.; Aube, J. "Asymmetric Schmidt Reaction of Hydroxyalkyl Azides with Ketones" *J. Am. Chem. Soc.,* **2003**, *125*, 7914.

(43) Edmonds, M. K.; Abell, A. D. "Design and Synthesis of a Conformationally Restricted Trans Peptide Isostere Based on the Bioactive Conformations of Saquinavir and Nelfinavir" *J. Org. Chem.*, **2001**, *66*, 3747.

(44) Faunce, J. A.; Grisso, B. A.; Mackenzie, P. B. "Enantioselective aldol chemistry via alkyl enol ethers. Scope of the Lewis acid catalyzed condensation of optically active trimethylsilyl and methyl 2-[(E)-1-alkenyloxy]ethanoates with acetals" *J. Am. Chem. Soc.*, **1991**, *113*, 3418.

(45) Hoang, G. L.; Takacs, J. M. "Enantioselective γ-borylation of unsaturated amides and stereoretentive Suzuki–Miyaura cross-coupling" *Chem. Sci.,* **2017**, *8*, 4511.

(46) Eno, M. S.; Lu, A.; Morken, J. P. "Nickel-Catalyzed Asymmetric Kumada Cross-Coupling of Symmetric Cyclic Sulfates" *J. Am. Chem. Soc.* **2016**, *138*, 7824.

(47) Lingam, V. S. P. R.; Thomas, A.; Dnyaneshwar-Harishchandra, D.; Rathi, V. E.; Khairatkar-Joshi, N.; Mukhopadhyay, I. *PCT Int. Appl.* **2014**, WO 2014016766 A1 Jan 30, 2014.

(48) Birman, V. B.; Li, X. "Benzotetramisole: A Remarkably Enantioselective Acyl Transfer Catalyst" *Org. Lett.*, **2008**, *8*, 1351.

(49) H. B. Kagan and J. C. Fiaud, *Topics in Stereochem.,* 1988, **18**, 249.